

WEST Search History

DATE: Tuesday, August 23, 2005

| Hide? | Set Name | Query | Hit Count |
|--------------------------|--------------------------------------------------------------------------|-----------------------------|-----------|
| | <i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i> | | |
| <input type="checkbox"/> | L21 | L19 and pancrea? | 1 |
| <input type="checkbox"/> | L20 | L2L19 and gemcitabine | 0 |
| <input type="checkbox"/> | L19 | L2 and antibod? | 6 |
| <input type="checkbox"/> | L18 | L13 and L15 | 3 |
| <input type="checkbox"/> | L17 | L13 and chemotherap? | 12 |
| <input type="checkbox"/> | L16 | L15 and gemcitabine | 1 |
| <input type="checkbox"/> | L15 | L13 and Her-2/neu | 3 |
| <input type="checkbox"/> | L14 | L13 and herceptin | 1 |
| <input type="checkbox"/> | L13 | L12 with donald.inv. | 25 |
| <input type="checkbox"/> | L12 | buchsbaum.inv. | 167 |
| <input type="checkbox"/> | L11 | L10 and chemo? | 0 |
| <input type="checkbox"/> | L10 | L8 and radiation | 2 |
| <input type="checkbox"/> | L9 | L8 and chemotherapeut? | 0 |
| <input type="checkbox"/> | L8 | Her-2/neu receptor antibod? | 2 |
| <input type="checkbox"/> | L7 | L2 and gemcitabine | 3 |
| <input type="checkbox"/> | L6 | L2 and chemotherapeu? | 0 |
| <input type="checkbox"/> | L5 | L2 with gemcitabine | 0 |
| <input type="checkbox"/> | L4 | L2 with cisplatin | 0 |
| <input type="checkbox"/> | L3 | L2 with chemotherapeu? | 0 |
| <input type="checkbox"/> | L2 | L1 with her-2/neu receptor | 6 |
| <input type="checkbox"/> | L1 | herceptin | 1181 |

END OF SEARCH HISTORY

WEST Search History

DATE: Tuesday, August 23, 2005

| Hide? | Set Name | Query | Hit Count |
|--------------------------|--------------------------------------------------------------------------|-------------------------------------|-----------|
| | <i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i> | | |
| <input type="checkbox"/> | L27 | L26 and pancrea? | 16 |
| <input type="checkbox"/> | L26 | L25 and colon | 40 |
| <input type="checkbox"/> | L25 | L24 and gemcitabine | 45 |
| <input type="checkbox"/> | L24 | L22 and herceptin | 129 |
| <input type="checkbox"/> | L23 | L22 and Her-2/neu receptor? | 3 |
| <input type="checkbox"/> | L22 | tumors with growth factor receptors | 2072 |
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| <input type="checkbox"/> | L17 | L13 and chemotherap? | 12 |
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| <input type="checkbox"/> | L13 | L12 with donald.inv. | 25 |
| <input type="checkbox"/> | L12 | buchsbaum.inv. | 167 |
| <input type="checkbox"/> | L11 | L10 and chemo? | 0 |
| <input type="checkbox"/> | L10 | L8 and radiation | 2 |
| <input type="checkbox"/> | L9 | L8 and chemotherapeut? | 0 |
| <input type="checkbox"/> | L8 | Her-2/neu receptor antibod? | 2 |
| <input type="checkbox"/> | L7 | L2 and gemcitabine | 3 |
| <input type="checkbox"/> | L6 | L2 and chemotherapeu? | 0 |
| <input type="checkbox"/> | L5 | L2 with gemcitabine | 0 |
| <input type="checkbox"/> | L4 | L2 with cisplatin | 0 |
| <input type="checkbox"/> | L3 | L2 with chemotherapeu? | 0 |
| <input type="checkbox"/> | L2 | L1 with her-2/neu receptor | 6 |
| <input type="checkbox"/> | L1 | herceptin | 1181 |

END OF SEARCH HISTORY

=> d his ful

FILE 'HCAPLUS' ENTERED AT 13:39:18 ON 23 AUG 2005

E BUCHSBAUM DONALD J/AU

L1 116 SEA ABB=ON ("BUCHSBAUM D J"/AU OR "BUCHSBAUM DONALD"/AU OR
 "BUCHSBAUM DONALD J"/AU OR "BUCHSBAUM DONALD JAY"/AU)
 L2 26 SEA ABB=ON L1 AND ?GROWTH?(W)?FACTOR?
 L3 10 SEA ABB=ON L2 AND ?RADIAT?
 L4 ANALYZE L3 6 CT : 13 TERMS

FILE 'REGISTRY' ENTERED AT 13:47:58 ON 23 AUG 2005

E HERCEPTIN/CN

L5 1 SEA ABB=ON HERCEPTIN/CN
 E HER-2/NEU/CN
 L7 4 SEA ABB=ON (PACLITAXEL OR GEMCITABINE OR 5-FLUOROURACIL OR
 DOXORUBICIN)/CN

FILE 'HCAPLUS' ENTERED AT 13:49:05 ON 23 AUG 2005

L8 1154 SEA ABB=ON (L5 OR ?HERCEPTIN? OR HER-2/NEU)
 L9 2811 SEA ABB=ON (L5 OR ?HERCEPTIN? OR HER-2)
 L10 2070 SEA ABB=ON L9 AND ?RECEPT?
 L11 950 SEA ABB=ON L10 AND ?ANTIBOD?
 L12 186 SEA ABB=ON L11 AND (L7 OR ?PACLITAXEL? OR ?GEMCITABINE? OR
 5(W)?FLUOROURACIL? OR ?DOXORUBIXIN?)
 L13 65 SEA ABB=ON L12 AND (?CANCER? OR ?CARCIN? OR ?NEOPLASM? OR
 ?TUMOR? OR ?TUMOUR?)(3A)(?PANCR? OR ?COLON?)
 L14 1 SEA ABB=ON L13 AND HER(W)2(W)NEU

FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 13:53:12 ON 23 AUG 2005

L15 2 SEA ABB=ON L14
 L16 2 DUP REMOV L15 (0 DUPLICATES REMOVED) *2 citi from above d.b.'s*

FILE 'USPATFULL' ENTERED AT 13:54:22 ON 23 AUG 2005

L17 245 SEA ABB=ON L13 AND HER(W)2(W)NEU
 L18 152 SEA ABB=ON L17 AND (PRD<20011207 OR PD<20011207)
 L19 2 SEA ABB=ON L18 AND ?COMB?(W)?RADIAT? *2 citi from USpatfull*

FILE 'HCAPLUS' ENTERED AT 13:57:43 ON 23 AUG 2005

L20 65 SEA ABB=ON L13 OR L14
 L21 35 SEA ABB=ON L20 AND (PRD<20011207 OR PD<20011207)
 L22 1 SEA ABB=ON L21 AND ?COMB?(W)?RADIAT?
 L23 3 SEA ABB=ON L21 AND ?RADIAT?
 L24 35 SEA ABB=ON L21 OR L22 OR L23 *35 citi from CAPLUS*

FILE HOME

FILE HCAPLUS

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FILE COVERS 1907 - 23 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 22 Aug 2005 (20050822/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2
DICTIONARY FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

FILE MEDLINE

FILE LAST UPDATED: 20 AUG 2005 (20050820/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 17 August 2005 (20050817/ED)

FILE RELOADED: 19 October 2003.

FILE EMBASE
FILE COVERS 1974 TO 18 Aug 2005 (20050818/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE JAPIO
FILE LAST UPDATED: 2 AUG 2005 <20050802/UP>
FILE COVERS APR 1973 TO APRIL 28, 2005

<<< GRAPHIC IMAGES AVAILABLE >>>

FILE JICST-EPLUS
FILE COVERS 1985 TO 22 AUG 2005 (20050822/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED
TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Aug 2005 (20050823/PD)
FILE LAST UPDATED: 23 Aug 2005 (20050823/ED)
HIGHEST GRANTED PATENT NUMBER: US6934966
HIGHEST APPLICATION PUBLICATION NUMBER: US2005183181
CA INDEXING IS CURRENT THROUGH 23 Aug 2005 (20050823/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Aug 2005 (20050823/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate

substance identification.

=> d que stat 124

L5 1 SEA FILE=REGISTRY ABB=ON HERCEPTIN/CN
 L7 4 SEA FILE=REGISTRY ABB=ON (PACLITAXEL OR GEMCITABINE OR
 5-FLUOROURACIL OR DOXORUBICIN)/CN
 L9 2811 SEA FILE=HCAPLUS ABB=ON (L5 OR ?HERCEPTIN? OR HER-2)
 L10 2070 SEA FILE=HCAPLUS ABB=ON L9 AND ?RECEPT?
 L11 950 SEA FILE=HCAPLUS ABB=ON L10 AND ?ANTIBOD?
 L12 186 SEA FILE=HCAPLUS ABB=ON L11 AND (L7 OR ?PACLITAXEL? OR
 ?GEMCITABINE? OR 5(W)?FLUOROURACIL? OR ?DOXORUBIXIN?)
 L13 65 SEA FILE=HCAPLUS ABB=ON L12 AND (?CANCER? OR ?CARCIN? OR
 ?NEOPLASM? OR ?TUMOR? OR ?TUMOUR?)(3A)(?PANCRA? OR ?COLON?)
 L14 1 SEA FILE=HCAPLUS ABB=ON L13 AND HER(W)2(W)NEU
 L20 65 SEA FILE=HCAPLUS ABB=ON L13 OR L14
 L21 35 SEA FILE=HCAPLUS ABB=ON L20 AND (PRD<20011207 OR PD<20011207)
 L22 1 SEA FILE=HCAPLUS ABB=ON L21 AND ?COMB?(W)?RADIAT?
 L23 3 SEA FILE=HCAPLUS ABB=ON L21 AND ?RADIAT?
 L24 35 SEA FILE=HCAPLUS ABB=ON L21 OR L22 OR L23

=> d ibib abs 124 1-35

L24 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:902199 HCAPLUS
 DOCUMENT NUMBER: 141:374704
 TITLE: Composition and uses of galectin antagonists to
 augment treatment of cancer or other proliferative
 disorders
 INVENTOR(S): Chang, Yan; Sasak, Vodek
 PATENT ASSIGNEE(S): Glycogenesys, Inc., USA
 SOURCE: PCT Int. Appl., 51 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------------|
| WO 2004091634 | A1 | 20041028 | WO 2004-US10675 | 20040407 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004023925 | A1 | 20040205 | US 2003-408723 | 20030407 <-- |
| US 2004223971 | A1 | 20041111 | US 2004-819901 | 20040407 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2003-408723 | A 20030407 |
| | | | US 2003-461006P | P 20030407 |
| | | | US 2003-474562P | P 20030530 |
| | | | US 2001-299991P | P 20010621 <-- |
| | | | US 2002-176235 | A2 20020620 |

AB The present invention is directed to methods and compns. for augmenting
 treatment of cancers and other proliferative disorders. In particular
 embodiments, the invention combines the administration of an agent that

inhibits the anti-apoptotic activity of galectin-3 (e.g., a 'galectin-3 inhibitor') so as to potentiate the toxicity of a chemotherapeutic agent. In certain preferred embodiments, the conjoint therapies of the present invention can be used to improve the efficacy of those chemotherapeutic agents whose cytotoxicity is influenced by the status of an anti-apoptotic Bcl-2 protein for the treated cell. For instance, galectin-3 inhibitors can be administered in combination with a chemotherapeutic agent that interferes with DNA replication fidelity or cell-cycle progression of cells undergoing unwanted proliferation.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:559502 HCAPLUS

DOCUMENT NUMBER: 141:190802

TITLE: Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors

INVENTOR(S): Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-yu; James, Ray A.; Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish A.

PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: U.S. Pat. Appl. Publ., 731 pp., Cont.-in-part of U.S. Ser. No. 85,896.

CODEN: USXXCO

DOCUMENT TYPE: Patent

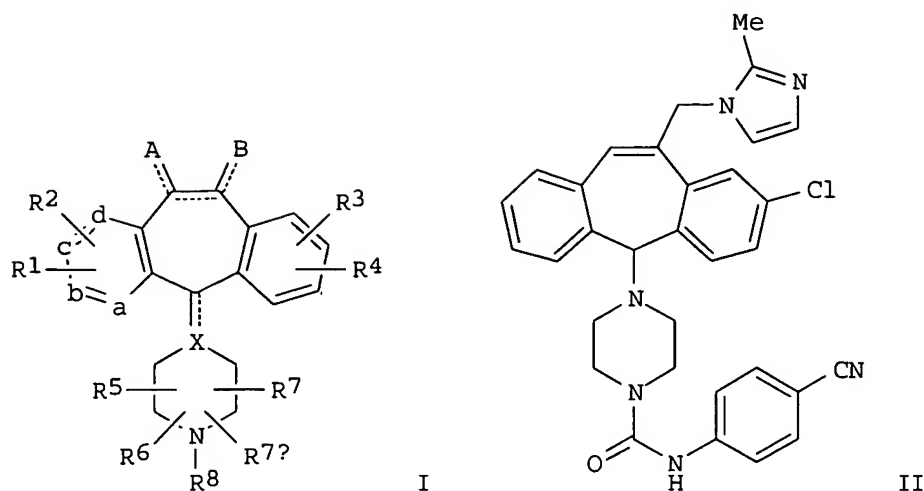
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-----------------|
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| US 2002198216 | A1 | 20021226 | US 2001-940811 | 20010828 <-- |
| US 2003229099 | A1 | 20031211 | US 2002-85896 | 20020227 <-- |
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-940811 | A2 20010828 <-- |
| | | | US 2002-85896 | A2 20020227 |
| | | | US 2002-325896 | A 20021219 |
| | | | US 2000-229183P | P 20000830 <-- |

GI



AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxy carbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocyclyl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung cancer cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as cancer.

L24 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:559501 HCAPLUS

DOCUMENT NUMBER: 141:106498

TITLE: Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors

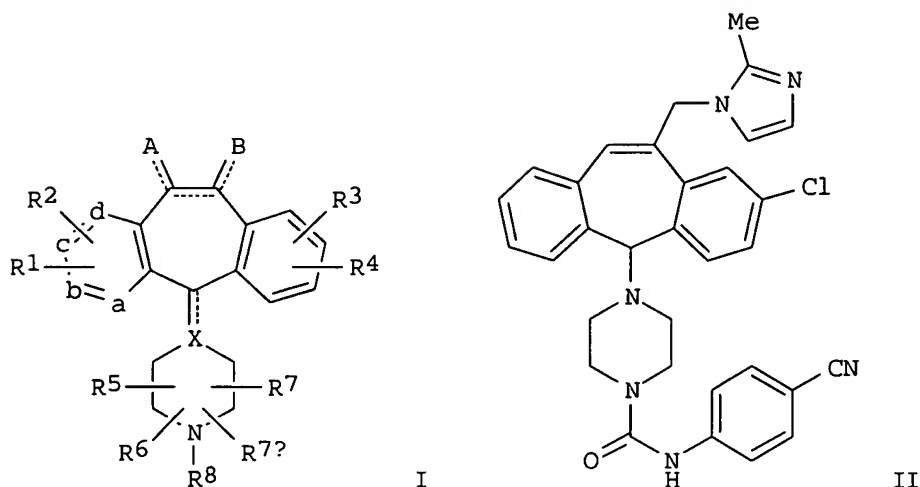
INVENTOR(S): Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-yu; James, Ray A.; Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish A.

PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: U.S. Pat. Appl. Publ., 731 pp., Cont.-in-part of U.S. Ser. No. 85,896.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 6
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-----------------|
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| US 2002198216 | A1 | 20021226 | US 2001-940811 | 20010828 <-- |
| US 2003229099 | A1 | 20031211 | US 2002-85896 | 20020227 <-- |
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-940811 | A2 20010828 <-- |
| | | | US 2002-85896 | A2 20020227 |
| | | | US 2002-325896 | A 20021219 |
| | | | US 2000-229183P | P 20000830 <-- |

GI



AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocycl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung cancer cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention

inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as cancer.

L24 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:533970 HCAPLUS
 DOCUMENT NUMBER: 141:65088
 TITLE: Methods and compositions for the prevention or treatment of neoplasia comprising a COX-2 inhibitor in combination with an epidermal growth factor **receptor** antagonist
 INVENTOR(S): Masferrer, Jaime
 PATENT ASSIGNEE(S): Pharmacia Corporation, USA
 SOURCE: U.S. Pat. Appl. Publ., 103 pp., Cont.-in-part of U.S. Ser. No. 470,951.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 21
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| US 2004127470 | A1 | 20040701 | US 2003-651916 | 20030829 <-- |
| EP 1522313 | A1 | 20050413 | EP 2004-26577 | 19991222 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY | | | | |
| WO 2005037259 | A2 | 20050428 | WO 2004-US27574 | 20040825 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.:
 US 1998-113786P P 19981223 <--
 US 1999-470951 B2 19991222 <--
 US 1999-385214 A 19990827 <--
 EP 1999-968939 A3 19991222 <--
 US 2003-651916 A 20030829

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGF **receptor** antagonist. Compns., pharmaceutical compns. and kits are also described.

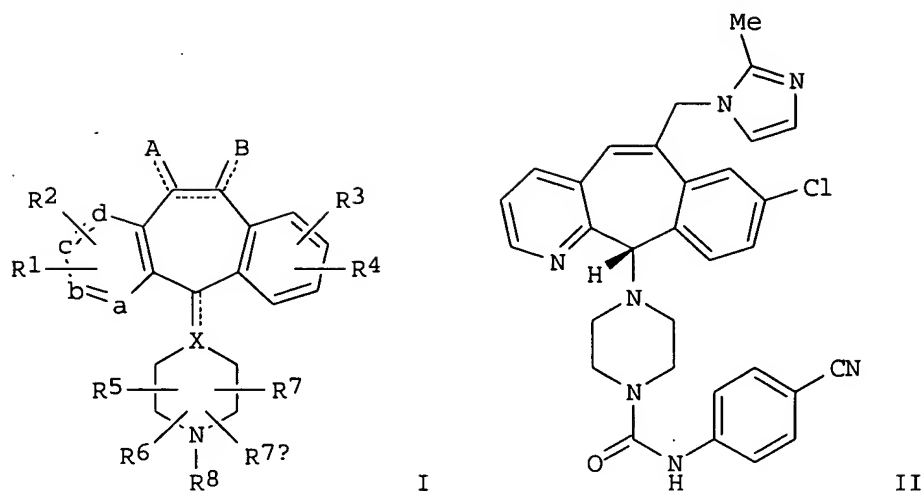
L24 ANSWER 5 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:513328 HCAPLUS
 DOCUMENT NUMBER: 141:71561
 TITLE: Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors
 INVENTOR(S): Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.;

Doll, Ronald J.; Girijavallabhan, Viyyoor M.;
 Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha;
 Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin,
 John J.; Li, Ge; Huang, Chia-yu; James, Ray A.;
 Bishop, W. Robert; Wang, James J.-S.; Desai, Jagdish
 A.

PATENT ASSIGNEE(S): Schering Corporation, USA
 SOURCE: U.S. Pat. Appl. Publ., 731 pp., Cont.-in-part of U.S.
 Ser. No. 85,896.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 6
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| US 2002198216 | A1 | 20021226 | US 2001-940811 | 20010828 <-- |
| US 2003229099 | A1 | 20031211 | US 2002-85896 | 20020227 <-- |
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |
| CA 2477328 | AA | 20030904 | CA 2003-2477328 | 20030225 |
| WO 2003072549 | A1 | 20030904 | WO 2003-US5479 | 20030225 |
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| MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, | | | | |
| SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM | | | | |
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| FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, | | | | |
| BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| BR 2003008071 | A | 20041221 | BR 2003-8071 | 20030225 |
| EP 1492772 | A1 | 20050105 | EP 2003-711214 | 20030225 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |
| IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-940811 | A2 20010828 <-- |
| | | | US 2002-85896 | A2 20020227 |
| | | | US 2000-229183P | P 20000830 <-- |
| | | | US 2002-325896 | A 20021219 |
| | | | WO 2003-US5479 | W 20030225 |
| OTHER SOURCE(S): MARPAT 141:71561 | | | | |
| GI | | | | |



AB Title benzo[5,6]cyclohepta[1,2-b]pyridines and analogs (I) [wherein one of a, b, d, e = N, N=O; remaining a, b, d, e = C substituted with R1 or R2; or each a, b, d, e = C substituted with R1 or R2; X = N, C, CH; A, B = independently H, (un)substituted R9, carbamoyl(alkyl), amino(alkyl), acylamino(alkyl), ureido(alkyl), etc.; R1-R4 = independently H, halo, CF3, alkoxy, amino, NO2, CN, alkyl, alkenyl, alkynyl, etc.; R5-R7a = independently H, CF3, acyl, alkyl, aryl; R8 = H, alkoxycarbonyl, aryloxy carbonyl, alkylsulfonyl, arylsulfonyl, etc.; R9 = (un)substituted heteroaryl(alkyl), arylalkoxy, heterocyclyl(alkyl), etc.; and stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs thereof] were prepared as farnesyl protein transferase (FPT) inhibitors. For example, a multi-step synthesis starting from tert-Bu 4-[8-chloro-6-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperazinecarboxylate, 2-methylimidazole, and p-cyanophenyl isocyanate gave (S)-II. The latter inhibited tumor growth of mouse H-Ras fibroblasts, HTB-177 human non-small cell lung cancer cells, and LOX human melanoma cells by 98% (60 MPK, p.o., BID, x2), 96% (80 MPK, p.o., BID, x3), and 90.3% (60 MPK, p.o., BID, x1), resp. Compds. of the invention inhibited FPT activity with IC50 values in the range of 0.05 nM to 100 nM and suppressed anchorage-independent growth of human tumor cells in a soft agar assay with IC50 values in the range of <0.5 nM to 50 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of proliferative diseases, such as cancer.

L24 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:100803 HCAPLUS

DOCUMENT NUMBER: 140:139483

TITLE: Method for enhancing the effectiveness of therapies of hyperproliferative diseases

INVENTOR(S): Chang, Yan; Sasak, Vodek

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 176,235.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|--------------|
| US 2004023925 | A1 | 20040205 | US 2003-408723 | 20030407 <-- |
| US 2003013681 | A1 | 20030116 | US 2002-176235 | 20020620 <-- |
| US 6680306 | B2 | 20040120 | | |
| CN 1543351 | A | 20041103 | CN 2002-816003 | 20020621 <-- |
| US 2004043962 | A1 | 20040304 | US 2003-657383 | 20030908 <-- |
| WO 2004091634 | A1 | 20041028 | WO 2004-US10675 | 20040407 |

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PRIORITY APPLN. INFO.: US 2001-299991P P 20010621 <--
US 2002-176235 A2 20020620
US 2003-408723 A 20030407
US 2003-461006P P 20030407
US 2003-474562P P 20030530

AB The efficacy of conventional cancer therapies such as surgery, chemotherapy and **radiation** is enhanced by the use of a therapeutic material which binds to and interacts with galectins. The therapeutic material can enhance apoptosis thereby increasing the effectiveness of oncolytic agents. It can also inhibit angiogenesis thereby moderating tumor growth and/or metastasis.

L24 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STM

ACCESSION NUMBER: 2003:971730 HCAPLUS

DOCUMENT NUMBER: 140:27844

TITLE: Preparation of tricyclic antitumor compounds as farnesyl protein transferase inhibitors

INVENTOR(S): Zhu, Hugh Y.; Njoroge, F. George; Cooper, Alan B.; Guzi, Timothy; Rane, Dinanath F.; Minor, Keith P.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Santhanam, Bama; Pinto, Patrick A.; Vibulbhan, Bancha; Keertikar, Kartik M.; Alvarez, Carmen S.; Baldwin, John J.; Li, Ge; Huang, Chia-Yu; James, Ray A.; Bishop, W. Robert; Wang, James J. S.; Desai, Jagdish A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 519 pp., Cont.-in-part of U.S. Pat. Appl. 2002 198,216.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|--------------|
| US 2003229099 | A1 | 20031211 | US 2002-85896 | 20020227 <-- |
| US 2002198216 | A1 | 20021226 | US 2001-940811 | 20010828 <-- |
| US 2004122018 | A1 | 20040624 | US 2002-325896 | 20021219 <-- |

US 2004122018 A1 20040624 US 2002-325896 20021219 <--
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CA 2477328 AA 20030904 CA 2003-2477328 20030225
WO 2003072549 A1 20030904 WO 2003-US5479 20030225
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BR 2003008071 A 20041221 BR 2003-8071 20030225
EP 1492772 A1 20050105 EP 2003-711214 20030225
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PRIORITY APPLN. INFO.: US 2000-229183P P 20000830 <--
US 2001-940811 A2 20010828 <--
US 2002-85896 A2 20020227
US 2002-325896 A 20021219
WO 2003-US5479 W 20030225
OTHER SOURCE(S): MARPAT 140:27844
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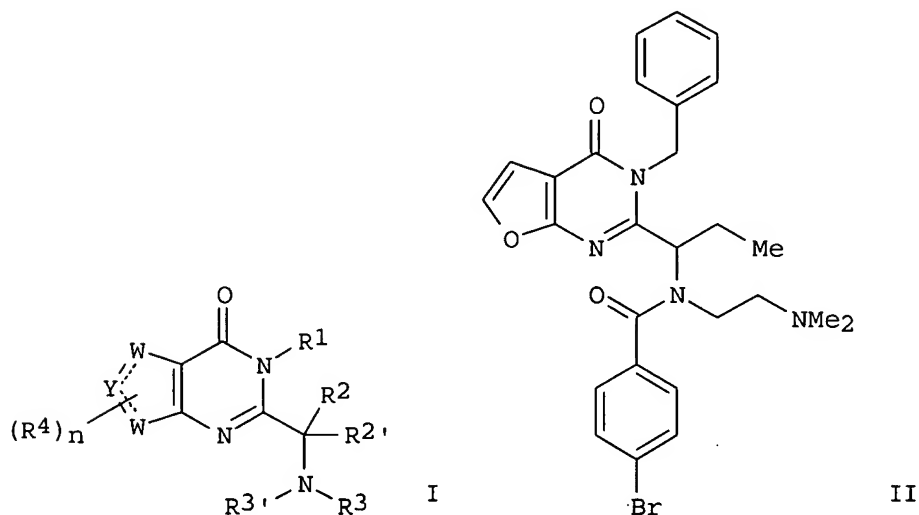
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; one of a, b, d, e = N, N:O; remaining a, b, d, e = C (wherein each C atom has an R1 or R2 bound to said carbon); or each a, b, d, e = C (wherein each C atom has an R1 or R2); R1-R4 = H, halo, CF3, alkoxy, etc.; R5-R7, R9 = H, CF3, alkyl, aryl, etc.; R8 = H, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, etc.; dotted line = single or double bond; X = N, CH; A, B = (un)substituted CH, CH2], their stereoisomers, pharmaceutically acceptable salts, solvates, and prodrugs which are useful for inhibiting farnesyl protein transferase, were prepared E.g., a multi-step synthesis of II, was given. The compds. I have an FTP IC50 in the range of 0.05 nM to 100 nM. Also disclosed are pharmaceutical compns. comprising title compds. I as well as methods of using them to treat proliferative diseases such as cancer.

L24 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:472516 HCAPLUS
DOCUMENT NUMBER: 139:53031
TITLE: Preparation of fuopyrimidinones as mitotic kinesin inhibitors for treatment of cancer
INVENTOR(S): Fraley, Mark E.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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WO 2003050122 A2 20030619 WO 2002-US38487 20021202 <--
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 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
 PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
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 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ,
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 CA 2467726 AA 20030619 CA 2002-2467726 20021202 <--
 EP 1465896 A2 20041013 EP 2002-799202 20021202 <--
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 JP 2005515208 T2 20050526 JP 2003-551146 20021202 <--
 US 2005032817 A1 20050210 US 2004-497382 20040601 <--
 PRIORITY APPLN. INFO.: US 2001-338380P P 20011206 <--
 WO 2002-US38487 W 20021202
 OTHER SOURCE(S): MARPAT 139:53031
 GI



AB Syntheses for title compds. I [wherein one of W, Y, or Z = O and the other 2 = CH; R¹ = H, perfluoroalkyl, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, aralkyl, or heterocyclyl; R², R^{2'}, R³, and R^{3'} = independently H, CO₂H, perfluoroalkyl, SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; or CR₂R_{2'} = (un)substituted (hetero)alkyl; or CR₃R_{3'} = (un)substituted heteroalkyl; R₄ = halo, OH, CN, CO₂H, perfluoroalkyl(oxy), SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; R₇ and R₈ = independently H, SO₂R_a, CON(R_b)₂, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, heterocyclyl, CO-Ob-(cyclo)alkyl, CO-Ob-alkenyl, CO-Ob-alkynyl,

CO-Ob-aryl, or CO-Ob-heterocyclyl; or NR7R8 = (un)substituted heterocyclyl; Ra = (cyclo)alkyl or heterocyclyl; Rb = H, (cyclo)alkyl, aryl, heterocyclyl, CO2-alkyl, CO-alkyl, or SO2Ra; a and b = independently 0-1; n = 0-2; and pharmaceutically acceptable salts or stereoisomers thereof] as KSP kinesin inhibitors are given (no data). For example, a detailed synthesis for the preparation of II is outlined. The scheme involves the reaction of tert-Bu 2-furylcarbamate with CO2 and benzylamine in the presence of t-BuLi, substitution with butyryl chloride, cyclization, bromination, addition of N,N-dimethylethylenediamine, and coupling with 4-bromobenzoyl chloride. I and pharmaceutical compns. thereof are useful for treating cellular proliferative diseases associated with KSP kinesin activity, such as cancer (no data).

L24 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:472471 HCAPLUS

DOCUMENT NUMBER: 139:69276

TITLE: Preparation of thienopyrimidines as mitotic kinesin inhibitors for the treatment of cancer

INVENTOR(S): Fraley, Mark E.; Hartman, George D.; Hoffman, William F.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 157 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

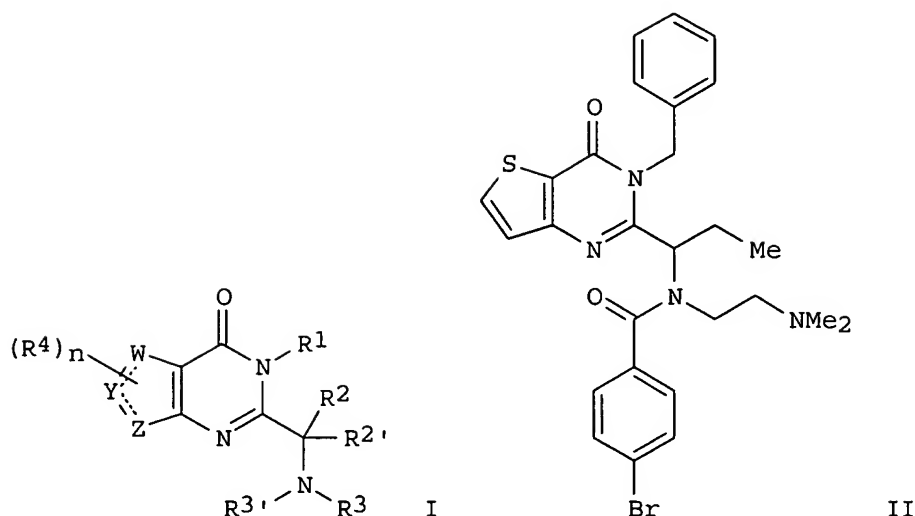
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2003050064 | A2 | 20030619 | WO 2002-US38417 | 20021202 <-- |
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| WO 2003050064 | B1 | 20031218 | | |
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| CA 2467722 | AA | 20030619 | CA 2002-2467722 | 20021202 <-- |
| EP 1463733 | A2 | 20041006 | EP 2002-804714 | 20021202 <-- |
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| JP 2005516007 | T2 | 20050602 | JP 2003-551092 | 20021202 <-- |
| PRIORITY APPLN. INFO.: | | | | |
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| | | | WO 2002-US38417 | W 20021202 |

OTHER SOURCE(S): MARPAT 139:69276

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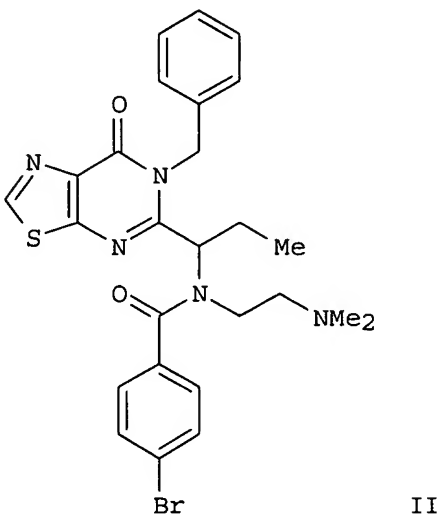
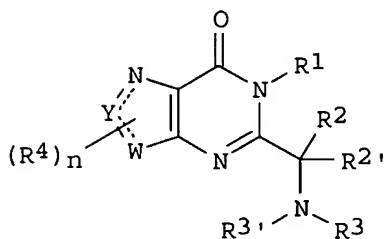


AB Title compds. I [wherein one of W, Y, or Z = S and the other 2 = CH; R1 = H, perfluoroalkyl, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, aralkyl, or heterocyclyl; R2, R2', R3, and R3' = independently H, CO₂H, perfluoroalkyl, SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; or CR₂R₂' = (un)substituted (hetero)alkyl; or CR₃R₃' = (un)substituted heteroalkyl; R4 = halo, OH, CN, CO₂H, perfluoroalkyl(oxy), SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; R7 and R8 = independently H, SO₂Ra, CON(Rb)₂, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, heterocyclyl, CO-Ob-(cyclo)alkyl, CO-Ob-alkenyl, CO-Ob-alkynyl, CO-Ob-aryl, or CO-Ob-heterocyclyl; or NR₇R₈ = (un)substituted heterocyclyl; Ra = (cyclo)alkyl or heterocyclyl; Rb = H, (cyclo)alkyl, aryl, heterocyclyl, CO₂-alkyl, CO-alkyl, or SO₂Ra; a and b = independently 0-1; n = 0-2; and pharmaceutically acceptable salts or stereoisomers thereof] were prepared for inhibiting KSP kinesin. For example, amidation of Me 3-aminothiophene-2-carboxylate with butyryl chloride afforded Me 3-(butyrylamino)thiophene-2-carboxylate, which was saponified to give the acid. Amidation with benzylamine, followed by cyclization provided 3-benzyl-2-propylthieno[3,2-d]pyrimidin-4(3H)-one. Bromination, coupling with N,N-dimethylethylenediamine, and reaction with 4-bromobenzoyl chloride gave the N-[1-(thienopyrimidinyl)propyl]benzamide II. The latter inhibited human poly-histidine tagged KSP motor domain with an IC₅₀ value of ≤50 μM. Thus, I and pharmaceutical compns. thereof are useful for treating cellular proliferative diseases associated with KSP kinesin activity, such as cancer (no data). Preparation of thienopyrimidine kinesin inhibitors from thiophenes, amines, and acid chlorides.

L24 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:472337 HCAPLUS
 DOCUMENT NUMBER: 139:69275
 TITLE: Preparation of thiazolopyrimidinones as mitotic kinesin inhibitors for treatment of cancer
 INVENTOR(S): Fraley, Mark E.; Hartman, George D.; Hoffman, William F.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 156 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------------|
| WO 2003049679 | A2 | 20030619 | WO 2002-US38313 | 20021202 <-- |
| WO 2003049679 | A3 | 20041007 | | |
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| CA 2468156 | AA | 20030619 | CA 2002-2468156 | 20021202 <-- |
| EP 1481077 | A2 | 20041201 | EP 2002-786830 | 20021202 <-- |
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| JP 2005520793 | T2 | 20050714 | JP 2003-550730 | 20021202 <-- |
| US 2005171122 | A1 | 20050804 | US 2003-497414 | 20021202 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-338344P | P 20011206 <-- |
| | | | WO 2002-US38313 | W 20021202 |
| OTHER SOURCE(S): | MARPAT 139:69275 | | | |
| GI | | | | |



AB Syntheses for title azolopyrimidinone compds. I [wherein Y = CH or N; W = CH, S, or O; R1 = H, perfluoroalkyl, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aralkyl, aryl, or heterocyclyl; R2, R2', R3, and R3' = independently H, perfluoroalkyl, CO₂H, SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl,

(CO)aOb-heterocyclyl, or SO₂-alkyl; or CR₂R₂' = (un)substituted (hetero)cyclyl; or NR₃R₃' = (un)substituted heterocyclyl; R₄ = independently halo, OH, CN, perfluoroalkyl(oxy), CO₂H, (CO)aNR₇R₈, SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; R₇ and R₈ = independently H, SO₂R_a, CON(R_b)₂, or (un)substituted CO-Ob-(cyclo)alkyl, CO-Ob-aryl, CO-Ob-heterocyclyl, (cyclo)alkyl, alkenyl, alkynyl, aryl, or heterocyclyl; or NR₇R₈ = (un)substituted heterocyclyl; R_a = (cyclo)alkyl, aryl, or heterocyclyl; R_b = H, (cyclo)alkyl, aryl, heterocyclyl, CO₂-alkyl, CO-alkyl, or SO₂R_a; a and b = independently 0-1; n = 0-2; and pharmaceutically acceptable salts or stereoisomers thereof] as KSP kinesin inhibitors are given (no data). For example, a detailed synthesis for the preparation of II is outlined (no data). The reaction scheme involves the cyclization of Et 5-amino-1,3-thiazole-4-carboxylate with tri-Me orthobutyrate and benzylamine to afford the [1,3]thiazolo[5,4-d]pyrimidin-7(6H)-one intermediate, followed by bromination, amination with N,N-dimethylethylenediamine, and amidation with 4-bromobenzoyl chloride. I and pharmaceutical compns. thereof are useful for treating cellular proliferative diseases associated with KSP kinesin activity, such as cancer (no data).

L24 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:472336 HCAPLUS

DOCUMENT NUMBER: 139:53029

TITLE: Preparation of cyclopenta[d]pyrimidinones as mitotic kinesin inhibitors for the treatment of cancer

INVENTOR(S): Fraley, Mark E.; Garbaccio, Robert M.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 135 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

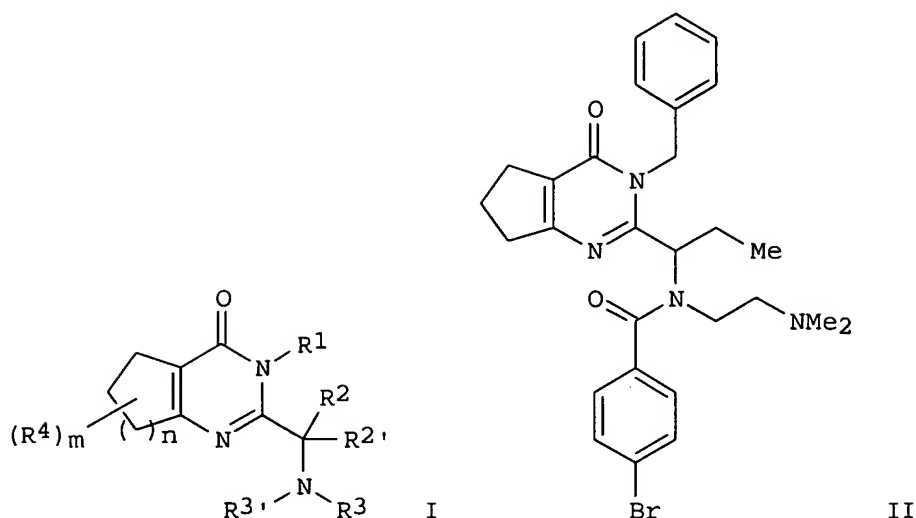
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2003049678 | A2 | 20030619 | WO 2002-US38312 | 20021202 <-- |
| WO 2003049678 | A3 | 20050519 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2468266 | AA | 20030619 | CA 2002-2468266 | 20021202 <-- |
| US 2005107404 | A1 | 20050519 | US 2003-497413 | 20021202 <-- |
| EP 1551812 | A2 | 20050713 | EP 2002-804712 | 20021202 <-- |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-338379P | P 20011206 <-- |
| | | | WO 2002-US38312 | W 20021202 |

OTHER SOURCE(S): MARPAT 139:53029

GI



AB Title compds. I [wherein one of R1 = H, perfluoroalkyl, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, aralkyl, or heterocyclyl; R2, R2', R3, and R3' = independently H, CO₂H, perfluoroalkyl, SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; or CR₂R₂' = (un)substituted (hetero)alkyl; or CR₃R₃' = (un)substituted heteroalkyl; R₄ = halo, OH, CN, CO₂H, perfluoroalkyl(oxy), SO₂NR₇R₈, or (un)substituted (CO)aOb-(cyclo)alkyl, (CO)aOb-alkenyl, (CO)aOb-alkynyl, (CO)aOb-aryl, (CO)aOb-heterocyclyl, or SO₂-alkyl; R₇ and R₈ = independently H, SO₂R_a, CON(R_b)₂, or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, aryl, heterocyclyl, CO-Ob-(cyclo)alkyl, CO-Ob-alkenyl, CO-Ob-alkynyl, CO-Ob-aryl, or CO-Ob-heterocyclyl; or NR₇R₈ = (un)substituted heterocyclyl; R_a = (cyclo)alkyl or heterocyclyl; R_b = H, (cyclo)alkyl, aryl, heterocyclyl, CO₂-alkyl, CO-alkyl, or SO₂R_a; a and b = independently 0-1; m = 0-3; n = 1-3; and pharmaceutically acceptable salts or stereoisomers thereof] were prepared for inhibiting KSP kinesin. For example, reaction of Et 2-aminocyclopentenecarboxylate with 1,1,1-trimethoxybutane and benzylamine gave 3-benzyl-2-propyl-3,5,6,7-tetrahydro-4H-cyclopenta[d]pyrimidin-4-one. Bromination, substitution with N,N-dimethylethylenediamine, and coupling with 4-bromobenzoyl chloride provided II. The latter inhibited human poly-histidine tagged KSP motor domain with an IC₅₀ value of ≤50 μM. Thus, I and pharmaceutical compns. thereof are useful for treating cellular proliferative diseases associated with KSP kinesin activity, such as cancer.

L24 ANSWER 12 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:472306 HCAPLUS
 DOCUMENT NUMBER: 139:47130
 TITLE: Azolopyrimidinone compound mitotic kinesin inhibitors for the treatment of proliferative diseases
 INVENTOR(S): Fraley, Mark E.; Hartman, George D.; Hoffman, William F.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 153 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------------|
| WO 2003049527 | A2 | 20030619 | WO 2002-US38488 | 20021202 <-- |
| WO 2003049527 | A3 | 20040304 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2467916 | AA | 20030619 | CA 2002-2467916 | 20021202 <-- |
| EP 1458726 | A2 | 20040922 | EP 2002-798478 | 20021202 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| JP 2005516000 | T2 | 20050602 | JP 2003-550582 | 20021202 <-- |
| US 2005176737 | A1 | 20050811 | US 2003-497385 | 20021202 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-338779P | P 20011206 <-- |
| | | | WO 2002-US38488 | W 20021202 |

OTHER SOURCE(S): MARPAT 139:47130

AB The invention provides azolopyrimidinone compds. that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The invention also provides compns. which comprise these compds., and methods of using them to treat cancer in mammals. Preparation of N-[1-(5-benzyl-3-bromo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)propyl]-4-bromo-N-[2-(dimethylamino)ethyl]benzamide is described.

L24 ANSWER 13 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:377149 HCAPLUS

DOCUMENT NUMBER: 138:362662

TITLE: EGF **receptor**-mediated signal modulation-based method for prediction or prognosis of the efficacy of a tumor treatment

INVENTOR(S): Waldenmaier, Dirk; Metzger, Rainer; Kischkel, Frank

PATENT ASSIGNEE(S): Cellcontrol Biomedical Laboratories AG, Germany

SOURCE: PCT Int. Appl., 106 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

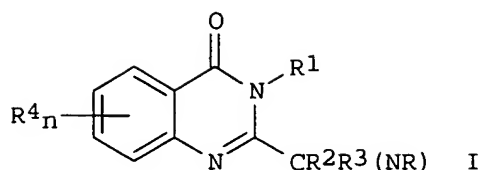
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2003040724 | A1 | 20030515 | WO 2002-EP12392 | 20021106 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

DE 10154540 A1 20030522 DE 2001-10154540 20011107
PRIORITY APPLN. INFO.: DE 2001-10154540 A 20011107 <--
AB A method for prediction or prognosis of the efficacy of a tumor treatment
is disclosed, comprising an interaction partner and a therapeutic agent,
the efficacy of which is predicted or prognosed by measuring a modulation
of an EGF **receptor**-mediated signal. The invention further
provides a method for identification and modification of interaction
partners and therapeutic agents for tumor treatment.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 14 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:376563 HCAPLUS
DOCUMENT NUMBER: 138:385439
TITLE: Preparation of quinazolinone mitotic kinesin
inhibitors for treating cancer
INVENTOR(S): Fraley, Mark E.; Hoffman, William F.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2003039460 | A2 | 20030515 | WO 2002-US35111 | 20021101 <-- |
| WO 2003039460 | A3 | 20030731 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2465491 | AA | 20030515 | CA 2002-2465491 | 20021101 <-- |
| EP 1444209 | A2 | 20040811 | EP 2002-799174 | 20021101 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| JP 2005511581 | T2 | 20050428 | JP 2003-541752 | 20021101 <-- |
| US 2004259826 | A1 | 20041223 | US 2004-494899 | 20040507 <-- |
| PRIORITY APPLN. INFO.: US 2001-344453P P 20011107 <-- | | | | |
| OTHER SOURCE(S): WO 2002-US35111 W 20021101 | | | | |
| GI | | | | |



AB The present invention relates to quinazolinones (shown as I; variables defined below; e.g. 3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one) that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The invention also related to compns. which comprise these compds., and methods of using them to treat cancer in mammals. Twelve examples of I were found in a kinesin ATPase in vitro assay to have $IC_{50} \leq 50 \mu M$. Although the methods of preparation are not claimed, 1 example preparation of I and characterization data for another 10 examples of I are included. For I: NR = 5-12 membered N-containing heterocycle, which is optionally substituted with 1-6 R5 groups and which optionally incorporates 1-2 addnl. heteroatoms = N, O and S in the heterocycle; a = 0, 1; b = 0, 1; m = 0-2; n = 0-4; R1 = H, C1-C10 alkyl, aryl, C2-C10 alkenyl, C2-C10 alkynyl, C1-C6 perfluoroalkyl, C3-C8 cycloalkyl, and heterocyclyl. R2 and R3 = H, (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, C1-C6 perfluoroalkyl, (C:O)aObC3-C8 cycloalkyl, (C:O)aObheterocyclyl, SO2NR7R8, and SO2C1-C10 alkyl; R4 = (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, (C:O)aObheterocyclyl, SO2NR7R8, and SO2C1-C10 alkyl; R5 is (C:O)aObC1-C10 alkyl, (C:O)aObaryl, C2-C10 alkenyl, C2-C10 alkynyl, (C:O)aOb heterocyclyl, CO2H, halo, CN, OH, ObC1-C6 perfluoroalkyl, Oa(C:O)bNR7R8, oxo, CHO, N(O)R7R8, or C(O)aObC3-C8 cycloalkyl; addnl. details are given in the claims.

L24 ANSWER 15 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:219666 HCAPLUS

DOCUMENT NUMBER: 138:231716

TITLE: Valproic acid and derivatives thereof for the combination therapy of human cancers, for the treatment of tumor metastasis and minimal residual disease

INVENTOR(S): Heinzl, Thorsten; Gottlicher, Martin; Hentsch, Bernd; Wels, Winfried Stephan; Pelicci, Pier Giuseppe; Minucci, Saverio; Herrlich, Peter A.; Groner, Bernd

PATENT ASSIGNEE(S): G2M Cancer Drugs AG, Germany

SOURCE: Eur. Pat. Appl., 61 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------|
| EP 1293205 | A1 | 20030319 | EP 2001-121722 | 20010918 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |

CA 2460713 AA 20030327 CA 2002-2460713 20020917 <--
 WO 2003024442 A2 20030327 WO 2002-EP10419 20020917 <--
 WO 2003024442 A3 20030918
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 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
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 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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 EP 1427403 A2 20040616 EP 2002-777129 20020917 <--
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 EP 1529527 A2 20050511 EP 2005-101081 20020917 <--
 EP 1529527 A3 20050525
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 IE, FI, CY, TR, BG, CZ, EE, SK
 JP 2005512961 T2 20050512 JP 2003-528538 20020917 <--
 US 2005038113 A1 20050217 US 2004-489770 20041029 <--
 PRIORITY APPLN. INFO.: EP 2001-121722 A 20010918 <--
 EP 2002-777129 A3 20020917
 WO 2002-EP10419 W 20020917

OTHER SOURCE(S): MARPAT 138:231716

AB The invention discloses the use of valproic acid and derivs. thereof as inhibitors of enzymes having histone deacetylase activity for the therapeutic treatment of human cancers in combination with established therapeutic principles. The invention also discloses the use of these compds. for the treatment of tumor metastasis and minimal residual disease. The invention includes the manufacture of a clin. used substance for the treatment of human cancers.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:202621 HCAPLUS

DOCUMENT NUMBER: 138:238027

TITLE: Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors

INVENTOR(S): Peckham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

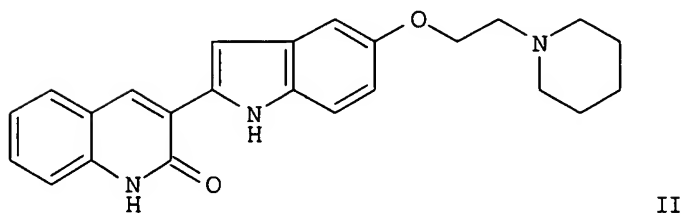
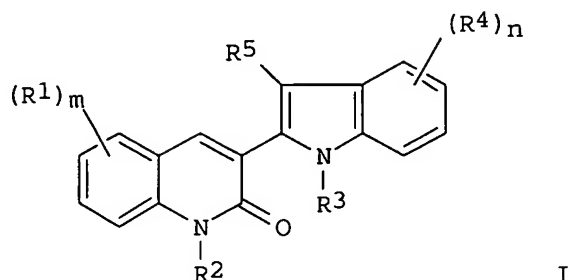
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|--------------|
| WO 2003020699 | A2 | 20030313 | WO 2002-US27114 | 20020826 <-- |
| WO 2003020699 | A3 | 20030522 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, | | | |

LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004235826 A1 20041125 US 2004-487589 20040224 <--
 PRIORITY APPLN. INFO.: US 2001-316123P P 20010830 <--
 WO 2002-US27114 W 20020826

GI



AB Title compds., including I (R groups undefined), were prepared and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-[(tert-butyltrimethylsilyl)oxy]-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (preparation of starting materials given) in the presence of Pd(PPh₃)₄ and K₃PO₄ in dioxane to give the protected 3-(2-indolyl)quinoline derivative. Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine•HCl and Cs₂CO₃ in DMF followed by reflux at 110° in AcOH and H₂O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC₅₀ values between 0.01 μM - 5.0 μM. Thus, I and compns. containing I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

L24 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:154204 HCAPLUS

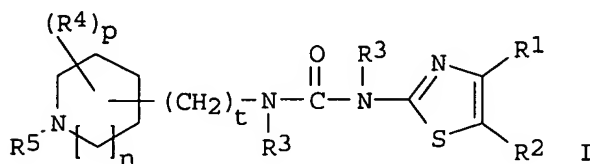
DOCUMENT NUMBER: 138:165738

TITLE: Tyrosine kinase inhibitors and their use in disease treatment

INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.;
 Smith, Anthony M.; Lumma, William C., Jr.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 58 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------------|
| WO 2003015717 | A2 | 20030227 | WO 2002-US27149 | 20020813 <-- |
| WO 2003015717 | A3 | 20031127 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004242637 | A1 | 20041202 | US 2004-487166 | 20040217 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-313374P | P 20010817 <-- |
| | | | WO 2002-US27149 | W 20020813 |

OTHER SOURCE(S): MARPAT 138:165738
 GI



AB The present invention relates to compds. I ($n = 1, 2, 3$; $p, t = 1, 2$; $R_1 = H$, halo, C1-8-alkyl; $R_2 = Ph$, CN, C(:O)NRaRb, halo, C3-6-cycloalkyl, C.tplbond.CRc; $R_4 = H$, halo, OH, C1-8-alkyl, C1-8-alkoxy; $R_5 = H$, Ph, C1-8-alkyl, CO2Rd, C(:O)Rd, SO2Rd; Ra, Rb = H, Ph, C1-8-alkyl, CO2Rd, C(:O)Rd, SO2Rd; Rc = H, Ph, C1-8-alkyl; Rd = Ph, C1-8-alkyl, benzyl) which inhibit, regulate and/or modulate tyrosine kinase signal transduction. I may be used to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. Thus, compds. such as N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea were prepared and tested for effects on VEGF **receptor** kinase, FLT-1 kinase, and HUVEC mitogenesis. I compds. inhibited HUVEC mitogenesis with IC50 values of 0.01-5.0 μM .

L24 ANSWER 18 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

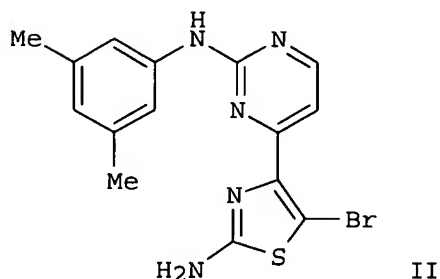
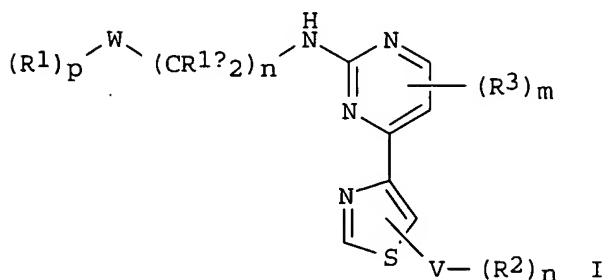
ACCESSION NUMBER: 2003:117808 HCAPLUS

DOCUMENT NUMBER: 138:170248

TITLE: Preparation of 4-(thiazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors

INVENTOR(S): Fraley, Mark E.; Hoffman, William F.; Hartman, George D.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 97 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------------------|-----------------|----------------|
| WO 2003011838 | A1 | 20030213 | WO 2002-US23882 | 20020727 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004181066 | A1 | 20040916 | US 2004-485291 | 20040129 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-309407P | P 20010801 <-- |
| | | | WO 2002-US23882 | W 20020727 |
| OTHER SOURCE(S): | | MARPAT 138:170248 | | |
| GI | | | | |



AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)CONR7R8, CO2R8,

(CH₂)_tSOO-2(CH₂)_tNR₇R₈, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R₃ = H, CN, halo, N(R₈)₂, OR₈, or (un)substituted (ar)alkyl or aryl; R₇ = H or (un)substituted (ar)alkyl; R₈ = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR₇R₈ = (un)substituted heterocyclyl; R₉ = independently (un)substituted alkyl, heterocyclyl, or aryl; W = aryl or heterocyclyl; m = 0-2; n = independently 0-6; p = 0-4; t = independently 0-6; or pharmaceutically acceptable salts, hydrates, or stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, cyclization of 2-bromo-1-[2-(methylthio)pyrimidin-4-yl]ethanone (3-step preparation given) with thiourea in EtOH gave 5-bromo-4-[2-(methylthio)pyrimidin-4-yl]-1,3-thiazol-2-amine•HBr. Oxidation to the methylsulfinyl derivative using oxone followed by substitution with 3,5-dimethylaniline afforded II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC values between 0.01 M and 5.0 M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age relate80d macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:117807 HCAPLUS

DOCUMENT NUMBER: 138:153548

TITLE: Preparation of 4-(pyrazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors

INVENTOR(S): Fraley, Mark E.; Peckham, Jennifer P.; Arrington, Kenneth L.; Hoffman, William F.; Hartman, George D.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 96 pp.

CODEN: PIXXD2

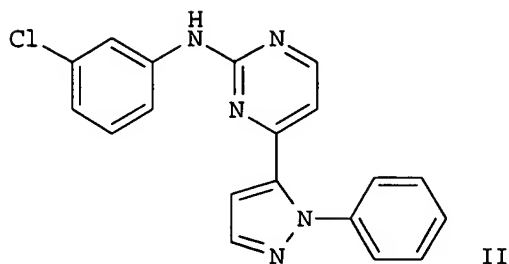
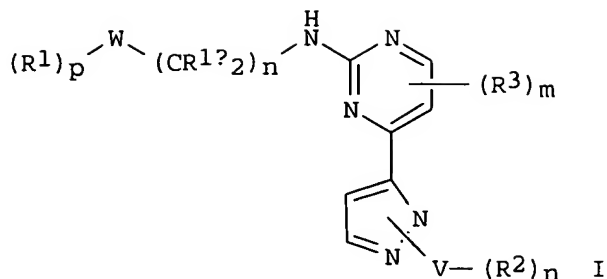
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2003011837 | A1 | 20030213 | WO 2002-US23879 | 20020726 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004235875 | A1 | 20041125 | US 2004-485296 | 20040129 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-309399P | P 20010801 <-- |
| | | | WO 2002-US23879 | W 20020726 |
| OTHER SOURCE(S): | | MARPAT 138:153548 | | |
| GI | | | | |



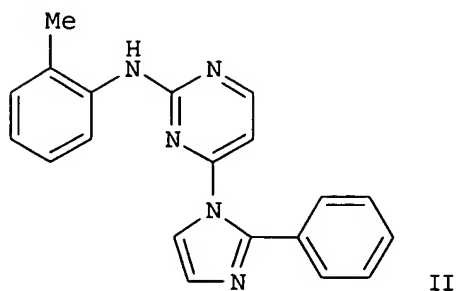
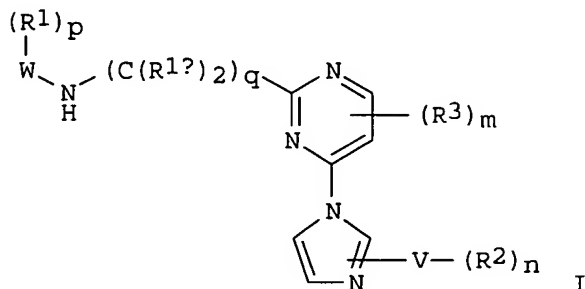
AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)tCONR7R8, CO2R8, (CH2)tSOO-2(CH2)tNR7R8, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R3 = independently H, CN, halo, N(R3)2, (CH2)tOR8, or (un)substituted (ar)alkyl or aryl; R7 = independently H or (un)substituted (ar)alkyl; R8 = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R9 = independently (un)substituted heterocyclyl, alkyl, or aryl; V = a bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-2; n = 0-6; p = 0-4; t = independently 0-6; and pharmaceutically acceptable salts, hydrates, and stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-(methylthio)pyrimidine-4-carboxylic acid was amidated with dimethylhydroxylamine•HCl in the presence of EDC and TEA, and the product treated with MeMgBr in Et2O to give 1-[2-(methylthio)pyrimidin-4-yl]ethanone. Coupling with N,N-dimethylformamide dimethylacetal followed by cyclization with phenylhydrazine afforded 2-(methylthio)-4-(1-phenyl-1H-pyrazol-3/5-yl)pyrimidine. Oxidation with oxone and reaction with 3-chloroaniline provided the 4-(pyrazolyl)-2-pyrimidinamine II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 μM and 5.0 μM. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:117806 HCAPLUS
 DOCUMENT NUMBER: 138:153547
 TITLE: Preparation of 4-(imidazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors
 INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Balitza,

Adrienne; Rodman, Leonard; Hartman, George D.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 105 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------------------|-----------------|----------------|
| WO 2003011836 | A1 | 20030213 | WO 2002-US23764 | 20020726 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004220201 | A1 | 20041104 | US 2004-485170 | 20040129 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-309400P | P 20010801 <-- |
| | | | WO 2002-US23764 | W 20020726 |
| OTHER SOURCE(S): | | MARPAT 138:153547 | | |
| GI | | | | |



AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, or OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)tCONR7R8, CO2R8, (CH2)tSOq(CH2)tNR7R8, oxido, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R3 = H, CN, halo, N(R8)2, (CH2)tOR8, or

(un)substituted (ar)alkyl or aryl; R7 = independently H or (un)substituted (ar)alkyl; R8 = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R9 = independently (un)substituted heterocyclyl, alkyl, or aryl; V = bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-3; n = 0-6; p = 0-4; q = undefined; t = 0-6; or pharmaceutically acceptable salts, hydrates or stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-phenylimidazole was coupled with 4-chloro-2-(methylthio)pyrimidine in the presence of NaH in DMF and the product oxidized using sodium tungstate dihydrate and H2O2 in EtOAc to give 2-(methylsulfonyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine. Substitution with 2-methylaniline and purification by reverse phase chromatog. afforded II•TFA. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 μ M and 5.0 μ M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:97306 HCAPLUS

DOCUMENT NUMBER: 138:137303

TITLE: Preparation of fused heterocycle substituted aminothiazolecarbonitriles as tyrosine kinase inhibitors

INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Hartman, George D.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 84 pp.

CODEN: PIXXD2

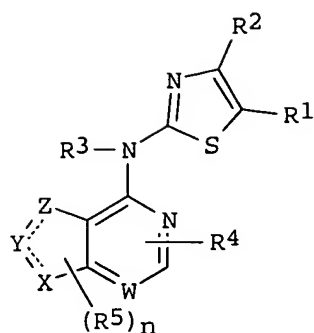
DOCUMENT TYPE: Patent

LANGUAGE: English

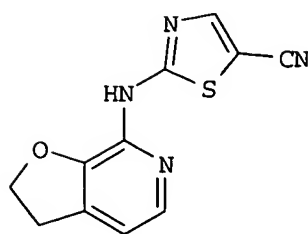
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2003009852 | A1 | 20030206 | WO 2002-US23191 | 20020719 <-- |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
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| US 2004235867 | A1 | 20041125 | US 2004-484986 | 20040123 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-307443P | P 20010724 <-- |
| | | | WO 2002-US23191 | W 20020719 |
| OTHER SOURCE(S): | MARPAT 138:137303 | | | |
| GI | | | | |



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II

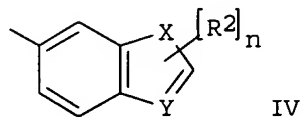
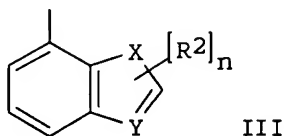
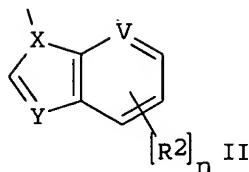
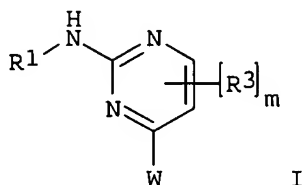
AB The present invention relates to the preparation of title compds. I (wherein X, Y, and Z = C, S, N, or O, provided that at least one of X, Y, or Z = C; W = C or N; n = 0-6; R1, R2, and R4 = independently H, perfluoroalkyl(oxy), OH, CN, halo, or (un)substituted (CO)rOs-alkyl, (CO)rOs-alkenyl, (CO)rOs-alkynyl, (CO)rOs-aryl, (CO)rOs-heterocyclyl, or alkyl-NRaRb; R3 = H, SO2Rc, (CO)rRc, or CO2Rc; R5 = R3 or Or(CO)sNRaRb, halo, OH, oxo, perfluoroalkyl(oxy), CHO, CO2H, CN, or (un)substituted (CO)rOs-aryl, (CO)rOs-heterocyclyl, or (CO)rOs-alkyl; r = 0-1; s = 0-1; Ra and Rb = independently H, SO2Rc, CO2Rc, or (un)substituted (CO)r-alkyl, (CO)r-heterocyclyl, or (CO)r-aryl; or NRaRb = (un)substituted monocyclic or bicyclic heterocycle; Rc = (un)substituted alkyl, aryl, benzyl, or heterocyclyl; or pharmaceutically acceptable salts or stereoisomers thereof], which inhibit, regulate, and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 7-bromofuro[2,3-c]pyridine was converted to the amine using benzophenone imine, NaOBu-t, racemic BINAP, and Pd2(dba)3 in dry toluene and then hydrogenated with 10% Pd/C in AcOH to give 2,3-dihydrofuro[2,3-c]pyridin-7-amine. Addition of 2-chloro-5-cyanothiazole in the presence of NaH in THF afforded the (furopyridinylamino)thiazolecarbonitrile II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001 μ M and 5.0 μ M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:977797 HCAPLUS
 DOCUMENT NUMBER: 138:55974
 TITLE: Preparation of 2-anilino-4-(indol-1-yl)pyrimidines as tyrosine kinase inhibitors
 INVENTOR(S): Kim, Yuntae; Hanney, Barbara
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 82 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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WO 2002102783 A1 20021227 WO 2002-US18907 20020614 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
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BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004171630 A1 20040902 US 2003-481370 20031219 <--
PRIORITY APPLN. INFO.: US 2001-299343P P 20010619 <--
WO 2002-US18907 W 20020614
OTHER SOURCE(S): MARPAT 138:55974
GI



AB The title compds. [I; W = II-IV; X, Y = C, N, provided that when X = N, then Y = C and when X = C, then Y = N; V = C, N; R1 = (un)substituted aryl, heterocyclyl; R2 = H, halo, alkyl, etc.; R3 = H, alkyl, aryl, etc.; m = 0-2; n = 0-5] which inhibit, regulate and/or modulate tyrosine kinase signal transduction, and therefore are useful in treating tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were prepared E.g., a multi-step synthesis of I [W = 4-fluoro-1H-indol-1-yl; R1 = Ph; R3 = H], starting from 2-thiouracil, was given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 23 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:940624 HCAPLUS

DOCUMENT NUMBER: 138:248543

TITLE: Nucleic acid treatment of diseases or conditions related to levels of Ras, HER2 and HIV

INVENTOR(S): McSwiggen, James

PATENT ASSIGNEE(S): Ribozyne Pharmaceuticals, Incorporated, USA

SOURCE: PCT Int. Appl., 185 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 211

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2002097114 | A2 | 20021205 | WO 2002-XA16840 | 20020529 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9851819 | A1 | 19980611 | AU 1998-51819 | 19980112 <-- |
| AU 729657 | B2 | 20010208 | | |
| AU 9939188 | A1 | 19990916 | AU 1999-39188 | 19990713 <-- |
| AU 769175 | B2 | 20040115 | AU 2000-56616 | 20000911 <-- |
| WO 2002097114 | A2 | 20021205 | WO 2002-US16840 | 20020529 <-- |
| WO 2002097114 | A3 | 20030508 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-294140P | P 20010529 <-- |
| | | | US 2001-296249P | P 20010606 <-- |
| | | | US 2001-318471P | P 20010910 <-- |
| | | | WO 2002-US16840 | A 20020529 |
| | | | AU 1995-26422 | A3 19950518 <-- |
| | | | US 1996-623891 | A 19960325 <-- |
| | | | AU 1996-76662 | A3 19961025 <-- |

AB The present invention relates to nucleic acid mols., including enzymic nucleic acid mols., such as DNazymes (e.g. DNA enzymes, catalytic DNA), siRNA, aptamers, and antisense that modulate the expression of Ras genes such as K-Ras, H-Ras, and/or N-Ras, HIV genes such as HIV-1, and HER2 (c-erbB2) gene. The sequence of human HER2 or Ras genes were screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary folding structure and contain potential enzymic nucleic acid mol. and/or antisense binding/cleavage sites are identified. The sequences of c-Ki-ras, c-Ha-ras, HER2, and HIV RNA binding/cleavage sites are provided, as are the sequences of designed enzymic nucleic acid mols., e.g., hammerhead ribozymes, DNazymes, inozymes, zinzymes, and Amberzymes. [This abstract record is one of 2 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.]

L24 ANSWER 24 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STM

ACCESSION NUMBER: 2002:927617 HCAPLUS

DOCUMENT NUMBER: 138:19530

TITLE: Nucleic acid treatment of diseases or conditions related to levels of Ras, HER2 and HIV

INVENTOR(S): McSwiggen, James

PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Incorporated, USA
 SOURCE: PCT Int. Appl., 185 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 211
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------------|
| WO 2002097114 | A2 | 20021205 | WO 2002-US16840 | 20020529 <-- |
| WO 2002097114 | A3 | 20030508 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| AU 9851819 | A1 | 19980611 | AU 1998-51819 | 19980112 <-- |
| AU 729657 | B2 | 20010208 | | |
| AU 9939188 | A1 | 19990916 | AU 1999-39188 | 19990713 <-- |
| AU 769175 | B2 | 20040115 | AU 2000-56616 | 20000911 <-- |
| WO 2002097114 | A2 | 20021205 | WO 2002-XA16840 | 20020529 <-- |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1390472 | A2 | 20040225 | EP 2002-734572 | 20020529 <-- |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| US 2003153521 | A1 | 20030814 | US 2002-238700 | 20020910 <-- |
| WO 2003070912 | A2 | 20030828 | WO 2003-US5045 | 20030220 <-- |
| WO 2003070912 | A3 | 20041111 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1501853 | A2 | 20050202 | EP 2003-716093 | 20030220 |
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| JP 2005517437 | T2 | 20050616 | JP 2003-569805 | 20030220 |
| US 2005080031 | A1 | 20050414 | US 2003-724270 | 20031126 <-- |
| US 2005176024 | A1 | 20050811 | US 2004-923354 | 20040820 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-294140P | P 20010529 <-- |

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| US 2001-296249P | P | 20010606 <-- |
| US 2001-318471P | P | 20010910 <-- |
| AU 1995-26422 | A3 | 19950518 <-- |
| US 1996-623891 | A | 19960325 <-- |
| AU 1996-76662 | A3 | 19961025 <-- |
| US 2001-292217P | P | 20010518 <-- |
| US 2001-306883P | P | 20010720 <-- |
| US 2001-916466 | A | 20010725 <-- |
| US 2001-311865P | P | 20010813 <-- |
| US 2002-358580P | P | 20020220 |
| US 2002-362016P | P | 20020306 |
| US 2002-363124P | P | 20020311 |
| WO 2002-US15876 | A2 | 20020520 |
| US 2002-157580 | A2 | 20020529 |
| WO 2002-US16840 | A | 20020529 |
| US 2002-163552 | A1 | 20020606 |
| US 2002-386782P | P | 20020606 |
| US 2002-393924P | P | 20020703 |
| US 2002-406784P | P | 20020829 |
| US 2002-408378P | P | 20020905 |
| US 2002-409293P | P | 20020909 |
| US 2002-238700 | A2 | 20020910 |
| US 2002-251117 | A1 | 20020919 |
| US 2002-277494 | A1 | 20021021 |
| US 2003-440129P | P | 20030115 |
| WO 2003-US5028 | A2 | 20030220 |
| WO 2003-US5045 | W | 20030220 |
| WO 2003-US5346 | A2 | 20030220 |
| US 2003-417012 | B2 | 20030416 |
| US 2003-422704 | B2 | 20030424 |
| US 2003-427160 | A2 | 20030430 |
| US 2003-444853 | A2 | 20030523 |
| US 2003-652791 | A2 | 20030829 |
| US 2003-693059 | A2 | 20031023 |
| US 2003-720448 | A2 | 20031124 |
| US 2003-724270 | A2 | 20031126 |
| US 2003-727780 | A2 | 20031203 |
| US 2004-757803 | A2 | 20040114 |
| US 2004-543480P | P | 20040210 |
| US 2004-780447 | A2 | 20040213 |
| US 2004-826966 | A2 | 20040416 |
| WO 2004-US13456 | A2 | 20040430 |
| WO 2004-US16390 | A2 | 20040524 |

AB The present invention relates to nucleic acid mols., including enzymic nucleic acid mols., such as DNAzymes (e.g. DNA enzymes, catalytic DNA), siRNA, aptamers, and antisense that modulate the expression of Ras genes such as K-Ras, H-Ras, and/or N-Ras, HIV genes such as HIV-1, and HER2 (c-erbB2) gene. The sequence of human HER2 or Ras genes were screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary folding structure and contain potential enzymic nucleic acid mol. and/or antisense binding/cleavage sites are identified. The sequences of c-Ki-ras, c-Ha-ras, HER2, and HIV RNA binding/cleavage sites are provided, as are the sequences of designed enzymic nucleic acid mols., e.g., hammerhead ribozymes, DNAzymes, inozymes, zinzymes, and Amberzymes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.]

L24 ANSWER 25 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:889451 HCAPLUS
 DOCUMENT NUMBER: 137:381947
 TITLE: Methods and reagents for the rapid and efficient isolation of circulating cancer cells
 INVENTOR(S): Terstappen, Leon W. M. M.; Rao, Galla Chandra; O'Hara, Shawn Mark; Liberti, Paul A.; Gross, Steven; Doyle, Gerald
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. 6,365,362.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| US 2002172987 | A1 | 20021121 | US 2002-79939 | 20020219 <-- |
| CA 2432361 | AA | 19990819 | CA 1999-2432361 | 19990212 <-- |
| CA 2432363 | AA | 19990819 | CA 1999-2432363 | 19990212 <-- |
| US 6365362 | B1 | 20020402 | US 1999-248388 | 19990212 <-- |
| US 2002009759 | A1 | 20020124 | US 2001-904472 | 20010713 <-- |
| US 6645731 | B2 | 20031111 | | |
| CA 2438112 | AA | 20030807 | CA 2002-2438112 | 20020219 <-- |
| WO 2003065042 | A1 | 20030807 | WO 2002-US5233 | 20020219 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
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| EP 1360496 | A1 | 20031112 | EP 2002-806645 | 20020219 <-- |
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| JP 2005516217 | T2 | 20050602 | JP 2003-564585 | 20020219 <-- |
| BR 2002007290 | A | 20050607 | BR 2002-7290 | 20020219 <-- |
| US 2003129676 | A1 | 20030710 | US 2002-269579 | 20021011 <-- |
| JP 2005010177 | A2 | 20050113 | JP 2004-265687 | 20040913 <-- |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1998-74535P | P 19980212 <-- |
| | | | US 1998-110202P | P 19981130 <-- |
| | | | US 1998-110279P | P 19981130 <-- |
| | | | US 1999-248388 | A2 19990212 <-- |
| | | | US 2001-268859P | P 20010216 <-- |
| | | | US 2001-269270P | P 20010220 <-- |
| | | | US 2001-269271P | P 20010220 <-- |
| | | | CA 1999-2320418 | A3 19990212 <-- |
| | | | JP 2000-531745 | A3 19990212 <-- |
| | | | US 2001-904472 | A1 20010713 <-- |
| | | | WO 2002-US5233 | W 20020219 |
| AB Methods and compns. are provided for detecting circulating tumor cells and assessing said cells for alterations in tumor-diathesis associated mols. Blood samples of women with stage III or metastatic breast cancer were reacted with anti-epithelial cell adhesion mol. monoclonal antibodies coupled to magnetic nanoparticles for immunomagnetic | | | | |

separation of epithelial cells from the blood. The separated cells were further reacted with phycoerythrin conjugated with anti-cytokeratin monoclonal **antibody** to cytokeratin, peridinin chlorophyll protein-labeled anti-CD45, and cyanine 5-labeled anti-**HER-2**. The samples were analyzed by FACS. The number of circulating tumor cells was determined and shown to be useful in assessing tumor progression.

L24 ANSWER 26 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:849467 HCAPLUS
 DOCUMENT NUMBER: 137:346156
 TITLE: Preventive/therapeutic method for cancer
 INVENTOR(S): Naito, Kenichiro; Furuya, Shuichi; Tasaka, Akihiro; Ban, Toshikazu
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 159 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------------|
| WO 2002087619 | A1 | 20021107 | WO 2002-JP4217 | 20020426 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2004002211 | A2 | 20040108 | JP 2002-127062 | 20020426 <-- |
| US 2004138160 | A1 | 20040715 | US 2004-475990 | 20040302 <-- |
| PRIORITY APPLN. INFO.: | | | JP 2001-131613 | A 20010427 <-- |
| | | | JP 2002-82019 | A 20020322 |
| | | | WO 2002-JP4217 | W 20020426 |

AB A method of preventing/treating cancer characterized by blocking the information signal of a polymer belonging to the epithelial growth factor **receptor** family by selectively inhibiting ErbB-2 (HER2).

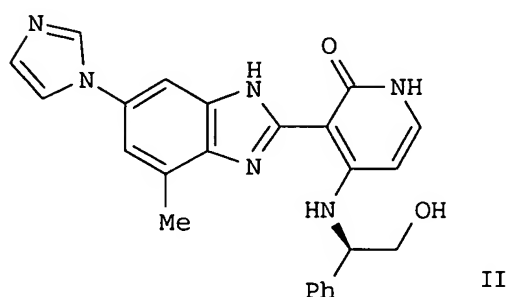
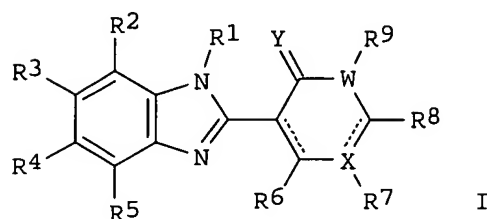
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 27 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:849373 HCAPLUS
 DOCUMENT NUMBER: 137:358081
 TITLE: Diagnostic imaging compositions, their methods of synthesis, and use
 INVENTOR(S): Li, Chun; Wen, Xiaoxia; Wu, Qing-Ping; Wallace, Sydney; Ellis, Lee M.
 PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
 SOURCE: PCT Int. Appl., 84 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2002087498 | A2 | 20021107 | WO 2002-US12510 | 20020419 <-- |
| WO 2002087498 | A3 | 20031030 | | |
| WO 2002087498 | C1 | 20031211 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW | | | | |
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| CA 2444483 | AA | 20021107 | CA 2002-2444483 | 20020419 <-- |
| US 2002197261 | A1 | 20021226 | US 2002-126369 | 20020419 <-- |
| US 2003003048 | A1 | 20030102 | US 2002-126216 | 20020419 <-- |
| EP 1389090 | A2 | 20040218 | EP 2002-766783 | 20020419 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| PRIORITY APPLN. INFO.: | | | US 2001-286453P | P 20010426 <-- |
| | | | US 2001-334969P | P 20011204 <-- |
| | | | US 2001-343147P | P 20011220 |
| | | | WO 2002-US12510 | W 20020419 |
| AB Conjugate mols. comprising a ligand bonded to a polymer are disclosed. One such conjugate mol. comprises a ligand bonded to a polymer, a chelating agent bonded to the polymer, and a radioisotope chelated to the chelating agent. The conjugate mols. may be useful in detecting and/or treating tumors or biol. receptors . These conjugate mols. may be synthesized without the necessity of preactivation of the ligand using an SCN-polymer-chelating agent precursor. Conjugate mols. incorporating an annexin V ligand are particularly useful for visualizing apoptotic cells. Conjugate mols. incorporating a C225 ligand are particularly useful for targeting tumors expressing EGFR. | | | | |
| L24 ANSWER 28 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN | | | | |
| ACCESSION NUMBER: | | 2002:777929 HCAPLUS | | |
| DOCUMENT NUMBER: | | 137:294954 | | |
| TITLE: | | Preparation of 2-(4-substituted-2-oxo-1,2-dihydropyridin-3-yl)-benzimidazoles as novel tyrosine kinase inhibitors | | |
| INVENTOR(S): | | Wittman, Mark D.; Balasubramanian, Neelakantan; Velaparthi, Upender; Zimmermann, Kurt; Saulnier, Mark G.; Liu, Peiying; Sang, Xiaopeng; Frennesson, David B.; Stoffan, Karen M.; Tarrant, James G. | | |
| PATENT ASSIGNEE(S): | | Bristol-Myers Squibb Company, USA | | |
| SOURCE: | | PCT Int. Appl., 249 pp. | | |
| | | CODEN: PIXXD2 | | |
| DOCUMENT TYPE: | | Patent | | |
| LANGUAGE: | | English | | |
| FAMILY ACC. NUM. COUNT: | | 2 | | |
| PATENT INFORMATION: | | | | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2002079192 | A1 | 20021010 | WO 2002-US9402 | 20020326 <-- |
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 CA 2442428 AA 20021010 CA 2002-2442428 20020326 <--
 EP 1381598 A1 20040121 EP 2002-723631 20020326 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 EE 200300475 A 20040216 EE 2003-475 20020326 <--
 CN 1514833 A 20040721 CN 2002-810516 20020326 <--
 JP 2004534010 T2 20041111 JP 2002-577817 20020326 <--
 BR 2002008373 A 20050222 BR 2002-8373 20020326 <--
 ZA 2003007466 A 20050113 ZA 2003-7466 20030925 <--
 NO 2003004308 A 20031126 NO 2003-4308 20030926 <--
 BG 108206 A 20041130 BG 2003-108206 20030926 <--
 PRIORITY APPLN. INFO.: US 2001-279327P P 20010328 <--
 WO 2002-US9402 W 20020326
 OTHER SOURCE(S): MARPAT 137:294954
 GI



AB The title compds. [I; X = N, C, a bond, etc.; Y = O, S; W = N, C, O, S (if W = O or S, then R9 is absent); R1-R9 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts which inhibit tyrosine kinase enzymes thereby making them useful as anti-cancer agents, were prepared Thus, reacting 3-[6-(imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one (preparation given) with (S)-(-)-2-phenylglycinol in the presence of N-methylmorpholine in DMF afforded 52% (S)-II which showed IC50 of 1.0 μ M in cytotoxicity assay (HT-29 human colon

tumor cell line). 30 Of the exemplified compds. I showed kinase activity of <25µM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. The compds. I are also useful for the treatment of other diseases which can be treated by inhibiting tyrosine kinase enzymes.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 29 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:637550 HCAPLUS
DOCUMENT NUMBER: 137:174955
TITLE: Targeted anti-tumor drug delivery systems
INVENTOR(S): Emanuel, David J.; Tendler, Craig L.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2002064168 | A1 | 20020822 | WO 2002-US4113 | 20020208 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002151508 | A1 | 20021017 | US 2002-67448 | 20020205 <-- |
| CA 2437768 | AA | 20020822 | CA 2002-2437768 | 20020208 <-- |
| EP 1359942 | A1 | 20031112 | EP 2002-714873 | 20020208 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004518717 | T2 | 20040624 | JP 2002-563960 | 20020208 <-- |
| PRIORITY APPLN. INFO.: US 2001-267807P P 20010209 <-- | | | | |
| WO 2002-US4113 W 20020208 | | | | |

AB Disclosed are methods for treating proliferative diseases, especially breast cancers, comprising administering (1) a therapeutically effective amount of a liposomal anthracycline composition in association with (2) a therapeutically effective amount of an **antibody** directed against the extracellular domain of a growth factor **receptor** and optionally in association with (3) a therapeutically effective amount of an addnl. antineoplastic agent. For example, the method comprises (1) administering PEGylated liposomal doxorubicin composition, followed by (2) cyclophosphamide, and (2) Trastuzumab (**antibody**).

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 30 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:449450 HCAPLUS
DOCUMENT NUMBER: 137:706
TITLE: **Combination radiation therapy and chemotherapy in conjunction with administration of growth factor receptor antibody**

INVENTOR(S) : Buchsbaum, Donald J.
 PATENT ASSIGNEE(S) : UAB Research Foundation, USA
 SOURCE: PCT Int. Appl., 16 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------------|
| WO 2002045653 | A2 | 20020613 | WO 2001-US46179 | 20011207 <-- |
| WO 2002045653 | A3 | 20030103 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002039486 | A5 | 20020618 | AU 2002-39486 | 20011207 <-- |
| US 2002076408 | A1 | 20020620 | US 2001-4833 | 20011207 <-- |
| PRIORITY APPLN. INFO.: | | | US 2000-251787P | P 20001208 <-- |
| | | | WO 2001-US46179 | W 20011207 |

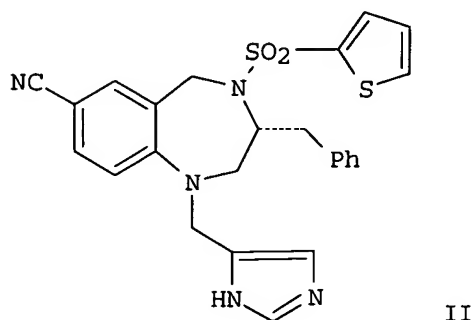
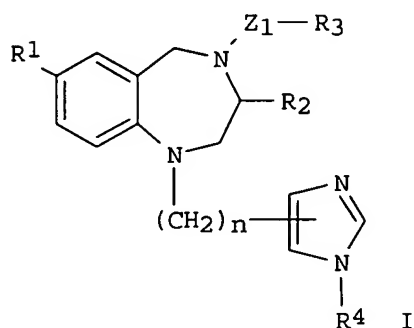
AB The invention comprises a method of inhibiting tumor growth in tumors having growth factor **receptors** comprising administering, about simultaneously, **antibodies** to the target growth factor **receptors**, at least one chemotherapeutic agent, and **radiation** therapy.

L24 ANSWER 31 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:730715 HCAPLUS
 DOCUMENT NUMBER: 135:288636
 TITLE: Synergistic methods and compositions for treating cancer using two or more anticancer agents
 INVENTOR(S) : Lee, Francis Y.
 PATENT ASSIGNEE(S) : Bristol-Myers Squibb Company, USA
 SOURCE: PCT Int. Appl., 81 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2001072721 | A2 | 20011004 | WO 2001-US9193 | 20010322 <-- |
| WO 2001072721 | A3 | 20020613 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

CA 2404712 AA 20011004 CA 2001-2404712 20010322 <--
 EP 1272193 A2 20030108 EP 2001-920653 20010322 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 JP 2003528864 T2 20030930 JP 2001-570634 20010322 <--
 US 2002002162 A1 20020103 US 2001-817456 20010326 <--
 US 6537988 B2 20030325
 NO 2002004610 A 20021125 NO 2002-4610 20020926 <--
 ZA 2002007766 A 20030120 ZA 2002-7766 20020926 <--
 PRIORITY APPLN. INFO.: US 2000-192278P P 20000327 <--
 WO 2001-US9193 W 20010322 <--
 OTHER SOURCE(S): MARPAT 135:288636
 GI



AB The present invention provides a synergistic method for the treatment of cancer which comprises administering a synergistically, therapeutically effective amount of: (i) at least agent selected from the group consisting of cytotoxic agents and cytostatic agents, and (ii) a compound of formula [I; R1 = Cl, Br, CN, substituted Ph, substituted pyridyl; R2 = alkyl, aralkyl; R3, R5 = substituted alkyl, aryl, heterocycle; R4 = H, alkyl; Z1 = CO, SO2, CO2, SO2N(R5); n = 1,2] or a pharmaceutically acceptable salt thereof. The present invention further provides a pharmaceutical composition for the synergistic treatment of cancer which comprises at least one agent selected from the group consisting of antiproliferative cytotoxic agents and antiproliferative cytostatic agents, a compound of formula I, and a pharmaceutically acceptable carrier. Synergism was observed when non-proliferating tumor cells were treated with diazepine II·HCl and **paclitaxel** (III) simultaneously or when III preceded II·HCl.

L24 ANSWER 32 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2001:167836 HCAPLUS
 DOCUMENT NUMBER: 134:221445
 TITLE: Dosages for treatment with anti-erbb2
antibodies
 INVENTOR(S): Baughman, Sharon Ann; Shak, Steven
 PATENT ASSIGNEE(S): Genentech, Inc., USA
 SOURCE: PCT Int. Appl., 71 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-------------------|-----------------|
| WO 2001015730 | A1 | 20010308 | WO 2000-US23391 | 20000825 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2382100 | AA | 20010308 | CA 2000-2382100 | 20000825 <-- |
| BR 2000013814 | A | 20020423 | BR 2000-13814 | 20000825 <-- |
| EP 1210115 | A1 | 20020605 | EP 2000-959423 | 20000825 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| TR 200200472 | T2 | 20020621 | TR 2002-200200472 | 20000825 <-- |
| JP 2003508447 | T2 | 20030304 | JP 2001-520142 | 20000825 <-- |
| US 6627196 | B1 | 20030930 | US 2000-648067 | 20000825 <-- |
| NZ 517150 | A | 20050128 | NZ 2000-517150 | 20000825 <-- |
| ZA 2002001229 | A | 20030416 | ZA 2002-1229 | 20020213 <-- |
| US 2004037824 | A1 | 20040226 | US 2003-600152 | 20030620 <-- |
| PRIORITY APPLN. INFO.: | | | US 1999-151018P | P 19990827 <-- |
| | | | US 2000-213822P | P 20000623 <-- |
| | | | US 2000-648067 | A3 20000825 <-- |
| | | | WO 2000-US23391 | W 20000825 <-- |

AB The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with anti-ErbB2 **antibody**.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 33 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2000:824125 HCAPLUS
 DOCUMENT NUMBER: 134:4050
 TITLE: Treatment with anti-erbb2 **antibodies**
 INVENTOR(S): Cohen, Robert L.
 PATENT ASSIGNEE(S): Genentech, Inc., USA
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2000069460 | A1 | 20001123 | WO 2000-US12552 | 20000509 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

CA 2374085 AA 20001123 CA 2000-2374085 20000509 <--
 EP 1187632 A1 20020320 EP 2000-928916 20000509 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 JP 2002544238 T2 20021224 JP 2000-617920 20000509 <--
 AU 782325 B2 20050721 AU 2000-47080 20000509 <--
 US 2003170235 A1 20030911 US 2003-429519 20030505 <--
 PRIORITY APPLN. INFO.: US 1999-134085P P 19990514 <--
 US 2000-568322 A1 20000509 <--
 WO 2000-US12552 W 20000509 <--

AB A method treating a human patient to or diagnosed with a tumor in which
 erbB2 protein is expressed comprising the following steps, performed
 sequentially: (a) treating the patient with a therapeutically effective
 amount of an anti-erbB2 **antibody**; (b) surgically removing the
 tumor, and then (c) treating the patient with a therapeutically effective
 amount of an anti-erbB2 **antibody** or of a chemotherapeutic agent.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 34 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2000:68356 HCAPLUS
 DOCUMENT NUMBER: 132:121460
 TITLE: Methods and compositions for cancer treatment
 INVENTOR(S): Marinkovich, Vincent
 PATENT ASSIGNEE(S): USA
 SOURCE: PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2000003733 | A1 | 20000127 | WO 1999-US15716 | 19990712 <-- |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9950970 | A1 | 20000207 | AU 1999-50970 | 19990712 <-- |
| US 2003108555 | A1 | 20030612 | US 2001-764224 | 20010116 <-- |
| PRIORITY APPLN. INFO.: US 1998-93084P P 19980716 <-- | | | | |
| WO 1999-US15716 W 19990712 <-- | | | | |

AB Compns., vaccines and kits for cancer immunotherapy are described. The
 compns., vaccines and kits may include transfer factor. The compns.,
 vaccines and kits also include modified monoclonal **antibodies**
 directed to cancer cells, other specific cancer **receptor**
 agonists, or viruses which infect cancer cells. The invention is also
 directed to methods of cancer immunotherapy using the compns. and vaccines
 of the invention.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:405000 HCAPLUS
 DOCUMENT NUMBER: 131:43591
 TITLE: Combination therapy of cancer with anti-ErbB2
antibodies
 INVENTOR(S): Shak, Steven; Paton, Virginia E.
 PATENT ASSIGNEE(S): Genentech, Inc., USA
 SOURCE: PCT Int. Appl., 42 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------------------------------------------------------------------------------------------|-----------------|
| WO 9931140 | A1 | 19990624 | WO 1998-US26266 | 19981210 <-- |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| ZA 9811162 | A | 20000607 | ZA 1998-11162 | 19981207 <-- |
| CA 2311409 | AA | 19990624 | CA 1998-2311409 | 19981210 <-- |
| AU 9919081 | A1 | 19990705 | AU 1999-19081 | 19981210 <-- |
| EP 1037926 | A1 | 20000927 | EP 1998-963840 | 19981210 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| TR 200001689 | T2 | 20010122 | TR 2000-200001689 | 19981210 <-- |
| BR 9815363 | A | 20011016 | BR 1998-15363 | 19981210 <-- |
| JP 2002508397 | T2 | 20020319 | JP 2000-539062 | 19981210 <-- |
| NZ 504597 | A | 20030530 | NZ 2000-504597 | 20000517 <-- |
| NO 2000002957 | A | 20000811 | NO 2000-2957 | 20000609 <-- |
| US 2003147884 | A1 | 20030807 | US 2003-356824 | 20030203 <-- |
| US 2004037823 | A9 | 20040226 | | |
| US 2003170234 | A1 | 20030911 | US 2003-406925 | 20030404 <-- |
| US 2005002928 | A1 | 20050106 | US 2004-909998 | 20040802 <-- |
| PRIORITY APPLN. INFO.: | | | US 1997-69346P | P 19971212 <-- |
| | | | US 1998-208649 | A3 19981210 <-- |
| | | | US 1998-209023 | A3 19981210 <-- |
| | | | WO 1998-US26266 | W 19981210 <-- |
| AB The authors disclose the treatment of disorders characterized by the overexpression of ErbB2. More specifically, human patients are treated with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline (e.g., doxorubicin or epirubicin). Preferably, the chemotherapeutic agent is Taxol. | | | | |
| REFERENCE COUNT: 6 | | | THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | |

=> d que stat 116

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L5          1 SEA FILE=REGISTRY ABB=ON  HERCEPTIN/CN
L7          4 SEA FILE=REGISTRY ABB=ON  (PACLITAXEL OR GEMCITABINE OR
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L9          2811 SEA FILE=HCAPLUS ABB=ON  (L5 OR ?HERCEPTIN? OR HER-2)
L10         2070 SEA FILE=HCAPLUS ABB=ON  L9 AND ?RECEPT?
L11         950 SEA FILE=HCAPLUS ABB=ON  L10 AND ?ANTIBOD?
L12        186 SEA FILE=HCAPLUS ABB=ON  L11 AND (L7 OR ?PACLITAXEL? OR
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L13         65 SEA FILE=HCAPLUS ABB=ON  L12 AND (?CANCER? OR ?CARCIN? OR
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L14         1 SEA FILE=HCAPLUS ABB=ON  L13 AND HER(W)2(W)NEU
L15         2 SEA L14
L16         2 DUP REMOV L15 (0 DUPLICATES REMOVED)

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=> d ibib abs 116 1-2

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L16  ANSWER 1 OF 2      MEDLINE on STN
ACCESSION NUMBER:      2004607491      MEDLINE
DOCUMENT NUMBER:       PubMed ID: 15581051
TITLE:                 Herceptin and gemcitabine for
                       metastatic pancreatic cancers that
                       overexpress HER-2/neu.
AUTHOR:                Safran Howard; Iannitti David; Ramanathan Ramesh; Schwartz
                       Jonathan D; Steinhoff Margaret; Nauman Chris; Hesketh Paul;
                       Rathore Ritesh; Wolff Robert; Tantravahi Umadevi; Hughes T
                       Marilyn; Maia Chris; Pasquariello Terry; Goldstein Lisa;
                       King Thomas; Tsai James Y; Kennedy Teresa
CORPORATE SOURCE:      The Brown University Oncology Group, Providence, Rhode
                       Island, USA.. hsafran@lifespan.org
CONTRACT NUMBER:       2P30 CA47904 (NCI)
                       5M01RR00056 (NCRR)
SOURCE:                Cancer investigation, (2004) 22 (5) 706-12.
                       Journal code: 8307154. ISSN: 0735-7907.
PUB. COUNTRY:         United States
DOCUMENT TYPE:         (CLINICAL TRIAL)
                       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:              English
FILE SEGMENT:          Priority Journals
ENTRY MONTH:           200412
ENTRY DATE:            Entered STN: 20041208
                       Last Updated on STN: 20041230
                       Entered Medline: 20041229
AB  PURPOSE: To determine the response rate and toxicities of
Herceptin and gemcitabine for patients with metastatic
pancreatic adenocarcinomas that overexpress HER
-2/neu. METHODS AND MATERIALS: Patients with
metastatic pancreatic cancer with 2+/3 + HER
-2/neu expression by immunohistochemistry were
eligible. Patients received gemcitabine, 1 g/m2/week, for 7 of
8 weeks followed by 3 of every 4 weeks, and Herceptin, 4 mg/kg
loading dose, followed by 2 mg/kg/week. RESULTS: Screening logs
demonstrated the rate of HER-2/neu
overexpression was 16%. Thirty-four patients were enrolled. Thirty
patients (88%) had pancreatic cancers with 2+
overexpression and 4 patients (12%) had 3+ overexpression. Toxicity was
similar to gemcitabine alone. Confirmed partial responses were
observed in 2 of 32 patients (6%). Thirteen of 32 patients (41%) had
either a partial response or a >50% reduction in CA 19-9. The median

```

survival for all 34 patients was 7 months, and the 1-year survival was 19%. CONCLUSION: The response rate of **Herceptin** and **gemcitabine** is similar to **gemcitabine** alone. The 7-month median survival in patients with metastatic **pancreatic cancer** suggests there may be a modest benefit for some patients. Infrequent **HER-2/neu** overexpression limits the role of targeting the **HER-2/neu** gene and prevents definitive conclusions on the addition of **Herceptin** to **gemcibine** for patients with **pancreatic cancer**.

L16 ANSWER 2 OF 2 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003250088 EMBASE

TITLE: Drug development in **pancreatic cancer**:
Finally, biology begets therapy.

AUTHOR: Cohen S.J.; Meropol N.J.

CORPORATE SOURCE: Dr. N.J. Meropol, 7701 Burholme Avenue, Philadelphia, PA
19111, United States. NJ_Meropol@fccc.edu

SOURCE: International Journal of Gastrointestinal Cancer, (2002)
Vol. 32, No. 2-3, pp. 91-106.

Refs: 130

ISSN: 0169-4197 CODEN: IJGCAJ

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20030710

Last Updated on STN: 20030710

AB **Pancreatic cancer** is rarely curable, and only 5% of patients achieve long-term survival. The vast majority of patients present with metastatic or unresectable disease. Standard chemotherapy with **gemcitabine** provides clinical benefit to only a small minority of patients. Thus, the development and investigation of new therapies is clearly needed. As knowledge of the underlying biology of **pancreatic cancer** has increased, targeted therapies based upon preclinical laboratory work have been developed, and are entering clinical trials. Some of these agents lack traditional dose-limiting toxicities (DLTs) at biologically active doses, and therefore clinical evaluation may not follow traditional guidelines for cytotoxic drug development. This article focuses on targeted therapies currently undergoing clinical evaluation in **pancreatic cancer**. Classes of therapeutics reviewed include those targeting tumor-microenvironment interactions (matrix metalloproteinase inhibitors, vascular endothelial growth-factor blockade), signal transduction (e.g., farnesyltransferase inhibitors), growth-factor **receptors** (epidermal growth-factor **receptor** blockade, **Her-2/neu**, gastrin), and vaccine approaches. Currently, there is a renewed optimism that the clinical application of biologic understanding will lead to an improved outcome for patients with **pancreatic cancer**.

=> d que stat 119

L5 1 SEA FILE=REGISTRY ABB=ON HERCEPTIN/CN
 L7 4 SEA FILE=REGISTRY ABB=ON (PACLITAXEL OR GEMCITABINE OR
 5-FLUOROURACIL OR DOXORUBICIN)/CN
 L9 2811 SEA FILE=HCAPLUS ABB=ON (L5 OR ?HERCEPTIN? OR HER-2)
 L10 2070 SEA FILE=HCAPLUS ABB=ON L9 AND ?RECEPT?
 L11 950 SEA FILE=HCAPLUS ABB=ON L10 AND ?ANTIBOD?
 L12 186 SEA FILE=HCAPLUS ABB=ON L11 AND (L7 OR ?PACLITAXEL? OR
 ?GEMCITABINE? OR 5(W)?FLUOROURACIL? OR ?DOXORUBIXIN?)
 L13 65 SEA FILE=HCAPLUS ABB=ON L12 AND (?CANCER? OR ?CARCIN? OR
 ?NEOPLASM? OR ?TUMOR? OR ?TUMOUR?)(3A)(?PANCR? OR ?COLON?)
 L17 245 SEA FILE=USPATFULL ABB=ON L13 AND HER(W)2(W)NEU
 L18 152 SEA FILE=USPATFULL ABB=ON L17 AND (PRD<20011207 OR PD<2001120
 7)
 L19 2 SEA FILE=USPATFULL ABB=ON L18 AND ?COMB?(W)?RADIAT?

=> d ibib abs 119 1-2

L19 ANSWER 1 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2003:99203 USPATFULL

TITLE: Methods of treating neoplasia with combination of
 target-cell specific adenovirus, chemotherapy and
 radiation

INVENTOR(S): Yu, De-Chao, Foster City, CA, UNITED STATES
 Chen, Yu, Cupertino, CA, UNITED STATES
 Henderson, Daniel R., Palo Alto, CA, UNITED STATES

| | NUMBER | KIND | DATE |
|---------------------|----------------|------|--------------|
| PATENT INFORMATION: | US 2003068307 | A1 | 20030410 |
| | US 6911200 | B2 | 20050628 |
| APPLICATION INFO.: | US 2001-814357 | A1 | 20010321 (9) |

| | NUMBER | DATE |
|-----------------------|----------------------------------------------------------------------------------------------|-------------------|
| PRIORITY INFORMATION: | US 2000-192015P | 20000324 (60) <-- |
| DOCUMENT TYPE: | Utility | |
| FILE SEGMENT: | APPLICATION | |
| LEGAL REPRESENTATIVE: | Debra J. Glaister, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018 | |
| NUMBER OF CLAIMS: | 58 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 42 Drawing Page(s) | |
| LINE COUNT: | 8142 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods of treating neoplasia using combinations
 of target cell-specific replication competent adenoviral vectors and
 chemotherapy, radiation therapy or combinations thereof. The adenoviral
 vectors are target cell-specific for the particular type of neoplasia
 for which treatment is necessary and the combination with the
 chemotherapy and/or radiation leads to synergistic treatment over
 existing adenoviral therapy or traditional chemotherapy and radiation
 therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L19 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2002:148271 USPATFULL

TITLE: **Combination radiation therapy and**

chemotherapy in conjunction with administration of
growth factor **receptor antibody**
INVENTOR(S): Buchsbaum, Donald J., Birmingham, AL, UNITED STATES

| | NUMBER | KIND | DATE |
|---------------------|---------------|------|---------------|
| PATENT INFORMATION: | US 2002076408 | A1 | 20020620 |
| APPLICATION INFO.: | US 2001-4833 | A1 | 20011207 (10) |

| | NUMBER | DATE |
|-----------------------|----------------------------------------------------------------------|-------------------|
| PRIORITY INFORMATION: | US 2000-251787P | 20001208 (60) <-- |
| DOCUMENT TYPE: | Utility | |
| FILE SEGMENT: | APPLICATION | |
| LEGAL REPRESENTATIVE: | Hendricks and Associates, P. O. Box 2509, Fairfax, VA, 22031-2509 | |
| NUMBER OF CLAIMS: | 13 | |
| EXEMPLARY CLAIM: | 1 | |
| LINE COUNT: | 446 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention comprises a method of inhibiting tumor growth in tumors having growth factor **receptors** comprising administering, about simultaneously, **antibodies** to the target growth factor **receptors**, at least one chemotherapeutic agent and radiation therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d ibib abs ind 13 1-10

L3 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:151613 HCAPLUS

DOCUMENT NUMBER: 142:309420

TITLE: Combined ionizing **radiation** and sKDR gene delivery for treatment of prostate carcinomas

AUTHOR(S): Kaliberov, S. A.; Kaliberova, L. N.; Buchsbaum, D. J.

CORPORATE SOURCE: Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

SOURCE: Gene Therapy (2005), 12(5), 407-417

CODEN: GETHEC; ISSN: 0969-7128

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Overexpression of vascular endothelial **growth factor**

(VEGF) and its cognate receptor KDR has been linked to a more aggressive phenotype of human prostate carcinomas. The importance of signal transduction through the VEGF receptor 2 is illustrated by use of soluble KDR, which binds to VEGF and sequesters this ligand before its binding to cellular receptor. Treatment with recombinant adenovirus AdVEGF-sKDR, encoding sKDR under control of the human VEGF promoter, significantly inhibited the proliferation of human vascular endothelial cells and prostate cancer cells. AdVEGF-sKDR infection decreased migration of endothelial 1P-1B cells (61% reduction) and DU145 prostate carcinoma cells (47%) in comparison with AdCMV-Luc-infected control cells. Ionizing **radiation** upregulated VEGF promoter activity in prostate carcinoma and endothelial cells. AdVEGF-sKDR infection significantly reduced human vascular endothelial and prostate cancer cell proliferation and sensitized cancer cells to ionizing **radiation**. In vivo tumor therapy studies demonstrated significant inhibition of DU145 tumor growth in mice that received combined AdVEGF-sKDR infection and ionizing **radiation** vs. AdVEGF-sKDR alone or **radiation** therapy alone. These results suggest that selective transcriptional targeting of sKDR gene expression employing a **radiation** inducible promoter can effectively inhibit tumor growth and demonstrate the advantage of combination radiotherapy and gene therapy for the treatment of prostate cancer.

CC 1-6 (Pharmacology)

Section cross-reference(s): 3

ST ionizing **radiation** sKDR gene therapy prostate cancer VEGF

IT Gene therapy

Genetic vectors

Human

Ionizing **radiation**

Prostate gland, neoplasm

Radiotherapy

(combined ionizing **radiation** and sKDR gene delivery for treatment of prostate carcinomas)

IT Promoter (genetic element)

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(combined ionizing **radiation** and sKDR gene delivery for treatment of prostate carcinomas)

IT Blood vessel

(endothelium; combined ionizing **radiation** and sKDR gene delivery for treatment of prostate carcinomas)

IT Vascular endothelial **growth factor** receptors

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);

THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type VEGFR-2; combined ionizing **radiation** and sKDR gene
delivery for treatment of prostate carcinomas)

IT Endothelium
(vascular; combined ionizing **radiation** and sKDR gene delivery
for treatment of prostate carcinomas)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1004497 HCAPLUS

DOCUMENT NUMBER: 142:106783

TITLE: Adenovirus-mediated FLT1-targeted proapoptotic gene
therapy of human prostate cancer

AUTHOR(S): Kaliberov, Sergey A.; Kaliberova, Lyudmila N.;
Stockard, Cecil R.; Grizzle, William E.;
Buchsbaum, Donald J.

CORPORATE SOURCE: Department of Radiation Oncology, University of
Alabama at Birmingham, Birmingham, AL, 35294, USA

SOURCE: Molecular Therapy (2004), 10(6), 1059-1070
CODEN: MTOHCK; ISSN: 1525-0016

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) is
of particular interest in the development of prostate carcinoma
therapeutics as it preferentially induces apoptosis of tumor cells. To
employ adenoviral vectors for highly efficient and specific TRAIL gene
transfer into cancer cells could overcome some potential problems for
recombinant TRAIL. The vascular endothelial **growth**
factor receptor FLT-1 is involved in regulation of angiogenesis
and tumor growth, invasion, and metastasis of prostate carcinoma. FLT-1
expression is observed in both tumor endothelial cells and prostate cancer
cells. We developed an adenoviral vector encoding the TRAIL gene under
control of the FLT1 promoter (AdFlt-TRAIL), which produced endothelial and
prostate cancer cell death. The combination of ionizing **radiation**
and adenovirus-driven TRAIL expression overcame human prostate cancer cell
resistance to TRAIL. Furthermore, in vivo administration of AdFlt-TRAIL
at the site of tumor growth in combination with **radiation**
treatment produced significant suppression of the growth of DU145 human
prostate tumor xenografts in athymic nude mice. Our results suggest that
specific TRAIL delivery employing the FLT1 promoter can effectively
inhibit tumor growth and demonstrate the advantage of combination
radiotherapy and gene therapy for the treatment of prostate cancer.

CC 1-6 (Pharmacology)

Section cross-reference(s): 3, 8

ST antiangiogenesis gene therapy prostate cancer TRAIL radiotherapy flt1
adenovirus

IT Proteins

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(TRAIL (tumor necrosis factor-related apoptosis-inducing ligand);
adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human
prostate cancer)

IT Angiogenesis inhibitors

Antitumor agents

Apoptosis

Gene therapy

Genetic vectors

Human

Human adenovirus

Radiotherapy

(adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human prostate cancer)

IT Promoter (genetic element)

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human prostate cancer)

IT Prostate gland, neoplasm

(carcinoma; adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human prostate cancer)

IT Vascular endothelial **growth factor** receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(gene, flt 1; adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human prostate cancer)

IT Carcinoma

(prostatic; adenovirus-mediated FLT1-targeted proapoptotic gene therapy of human prostate cancer)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:404840 HCAPLUS

DOCUMENT NUMBER: 142:129837

TITLE: Anti-EGFR-mediated radiosensitization as a result of augmented EGFR expression

AUTHOR(S): Bonner, James A.; Buchsbaum, Donald J.; Russo, Suzanne M.; Fiveash, John B.; Trummell, Hoa Q.; Curiel, David T.; Raisch, Kevin P.

CORPORATE SOURCE: Department of Radiation Oncology, Univ. Alabama Sch Med., Birmingham, AL, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2004), 59(2, Suppl.), 2-10
CODEN: IOBPD3; ISSN: 0360-3016

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Elevated epidermal **growth factor** receptor (EGFR) expression has correlated with a poor prognosis after standard treatment of several malignancies. However, it is not clear whether the absolute level of EGFR expression affects the radiosensitizing properties of anti-EGFR treatments. A better understanding of this question would be helpful for the design of protocols that deliver these treatments. To explore this question, cells (LS174T) that did not display inherent anti-EGFR treatment-induced radiosensitization were selected for studies that could potentially enhance EGFR expression. Human colon carcinoma cells (LS174T), which did not show radiosensitization by anti-EGFR treatments, were employed for these studies. (Also, these cells were not responsive to the antiproliferative effects of anti-EGFR treatment.). Using standard transfection techniques (eukaryotic expression vector) as well as an adenoviral construct to enhance EGFR expression, LS174T cells were transduced in a manner that resulted in enhanced expression of EGFR. Subsequently, standard proliferation studies were performed to test the radiosensitizing properties of anti-EGFR treatment (an anti-EGFR monoclonal antibody: IMC-C225). Studies were undertaken to stably transfect LS174T cells with EGFR. The stable transfectants, LS174T.EGFR cells, were responsive to the antiproliferative effects of anti-EGFR treatment, in contrast to the parent LS174T cells. Similar results were

demonstrated when the cells were infected with AdEGFR. Addnl., the LS174T.EGFR cells were responsive to the radiosensitizing properties of anti-EGFR treatment (IMC-C225), whereas the parent cells were not. Although the level of EGFR expression is of prognostic significance in many tumor models, the response of cells to anti-EGFR treatment alone, or combinations of this treatment with **radiation** or chemotherapy, depends upon many factors that are not necessarily related to the inherent EGFR expression of the tumor cells. However, the studies reported herein, demonstrate that when LS174T cells were transduced to show increased EGFR expression, they became responsive to the radiosensitizing properties of anti-EGFR treatments.

CC 8-9 (Radiation Biochemistry)
 Section cross-reference(s): 1
 ST EGFR antibody radiosensitizer radiotherapy
 IT Adenoviral vectors
 (AdEGFR; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Gene, animal
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (ERBB1; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Chemotherapy
 Human
 Radiosensitizers, biological
 Transformation, genetic
 (anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Epidermal **growth factor** receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Intestine, neoplasm
 (colon, carcinoma; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Carcinoma
 (colon; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Cell proliferation
 (inhibition; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (monoclonal, iodo, labeled with iodine-125, IMC-C225, anti-EGFR; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)
 IT Radiotherapy
 (targeted; anti-EGFR-mediated radiosensitization as result of augmented EGFR expression)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:523030 HCAPLUS

DOCUMENT NUMBER: 140:35435

TITLE: Differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody

AUTHOR(S): Huang, Zhi-qiang; Buchsbaum, Donald J.;

CORPORATE SOURCE: Raisch, Kevin P.; Bonner, James A.; Bland, Kirby I.;
Vickers, Selwyn M.
Department of Radiation Oncology, Department of
Surgery and Division of Radiation Biology, Division of
General Surgery, University of Alabama at Birmingham,
Birmingham, AL, USA

SOURCE: Journal of Surgical Research (2003), 111(2), 274-283
CODEN: JSGRA2; ISSN: 0022-4804

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background. Pancreatic cancer remains a devastating disease, with 95% of all patients diagnosed with the disease dying within 2 yr. The combined therapy using Erbitux, gemcitabine, and **radiation** caused complete tumor regression using a nude mouse model inoculated with pancreatic MiaPaCa-2 cells but only a delay in tumor growth with BxPC-3. We investigated the effect of prolonged Erbitux treatment to the sensitivity to gemcitabine and/or **radiation** and the epidermal **growth factor** receptor (EGFR) signal transduction pathway. MiaPaCa-2 and BxPC-3 cells were cultured with or without Erbitux for 6 wk. Cells were then treated with gemcitabine and/or **radiation**, harvested 48 h after treatment, and counted. Differences in EGFR expression after exposure to Erbitux were analyzed by FACS. Internalization rates of EGFR induced by Erbitux on these cell lines were determined using 125I-EGF binding assay after removal of Erbitux by acidic wash. Cell lysates were harvested after cells were stimulated with EGF, FGF, or IGF-1 resp., and EGFR was immunoprecipitated using Erbitux. Samples were separated using SDS-PAGE and transferred to PVDF membrane. The membranes were probed with antibody against human **growth factor** receptor binding protein (Grb2) to detect the association of this Ras-MAPK upstream adaptor protein to EGFR. Cell lysates were also separated with SDS-PAGE and probed with rabbit anti-human PARP after samples were transferred to PVDF membrane. Expression of BAX and Bcl-XL were probed in the cells treated with or without Erbitux. Proliferation assays indicated that prolonged exposure to Erbitux increased the sensitivities of MiaPaCa-2 to gemcitabine and **radiation** therapy ($41 \pm 16\%$ vs. $52 \pm 9\%$ for gemcitabine, 28 ± 9 vs. $39 \pm 9\%$ for combination; $P = 0.015$) but not for BxPC-3. FACS anal. showed that the expressed EGFR level decreased by about 42% on MiaPaCa 2 whereas no loss was seen on BxPC-3. Expression of BAX was upregulated on MiaPaCa-2. Poly (ADP-ribose) polymerase cleavage indicated the killing was mediated by apoptosis. Immunoblots showed that Grb2 was co-immunoprecipitated with EGFR after EGF stimulation. Incubation with Erbitux blocked Grb2 binding in MiaPaCa-2 but not BxPC 3. FGF transactivated EGFR downstream Ras-MAPK in the presence or absence of Erbitux. Internalization of EGFR induced by Erbitux did not differ between MiaPaCa-2 and BxPC-3. Conclusions. (1) Association of Grb2 to EGFR in BxPC-3 induced by EGF in the presence of Erbitux indicates an alternate pathway of Ras-MAPK activation, which may be related with the tumor resistance to treatment; (2) transactivation of EGFR downstream Ras-MAPK pathway by FGF contributes the resistance to treatment; and (3) downregulation of EGFR may increase the response to therapy.

CC 1-6 (Pharmacology)

Section cross-reference(s): 8, 15

ST pancreas carcinoma Erbitux EGFR antibody

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bax; differential responses by pancreatic carcinoma cell lines to
prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)

- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-xL; differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GRB-2 (**growth factor** receptor-bound protein 2);
differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Drug resistance
(antitumor; differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Pancreas, neoplasm
(carcinoma; differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Antitumor agents
Apoptosis
Drug interactions
Human
Radiotherapy
Signal transduction, biological
(differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Epidermal **growth factor** receptors
Ras proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Biological transport
(internalization; differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT Carcinoma
(pancreatic; differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT 142243-02-5, MAPK
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)
- IT 95058-81-4, Gemcitabine 205923-56-4, Erbitux
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erbitux (IMC-C225) anti-EGFR antibody)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:839606 HCAPLUS

DOCUMENT NUMBER: 139:32573

TITLE: Treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and radiation

AUTHOR(S): Buchsbaum, Donald J.; Bonner, James A.; Grizzle, William E.; Stackhouse, Murray A.; Carpenter,

Mark; Hicklin, Daniel J.; Bohlen, Peter; Raisch, Kevin P.
 CORPORATE SOURCE: Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
 SOURCE: International Journal of Radiation Oncology, Biology, Physics (2002), 54(4), 1180-1193
 CODEN: IOBPD3; ISSN: 0360-3016
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Purpose: To investigate treatment of human pancreatic cancer cell lines and xenografts with combinations of Erbitux (IMC-C225) anti-epidermal **growth factor** receptor (EGFR) antibody, gemcitabine, and **radiation**. Methods and Materials: BxPC-3 and MiaPaCa-2 human pancreatic carcinoma cells were treated in vitro for 24 h with IMC-C225 (5 µg/mL), then exposed to epidermal **growth factor** (EGF) (10 mM) for 5 min. Immunoblots were screened for EGFR expression and the ability of IMC-C225 to block EGF-induced tyrosine phosphorylation of EGFR. Cells were treated with IMC-C225 (5 µg/mL) on Day 0, the IC50 dose of gemcitabine on Day 1 for 24 h, followed by 3 Gy 60Co irradiation on Day 2, or the combination of each agent. For cell proliferation, cells were counted on Day 4, and for apoptosis, cells were stained with annexin V-FITC and propidium iodide, then analyzed by FACS. Cells were treated with the same single or multiple treatments and analyzed in a clonogenic cell survival assay. The effect of IMC-C225, gemcitabine, and **radiation** on the growth of BxPC-3 and MiaPaCa-2 tumor xenografts was determined. Athymic nude mice bearing established s.c. tumor xenografts of 6-8 mm diameter received 6 wk of treatment with IMC-C225 (1 mg every 3 days + 6) alone or in combination with gemcitabine (120 mg/kg i.v. every 6 days + 6), and 6 weekly fractions of 3 Gy **radiation** on the days after gemcitabine administration. Tumor growth was measured with Vernier calipers. Results: BxPC-3 and MiaPaCa-2 cell lines expressed low levels of EGFR. IMC-C225 inhibited EGF-induced tyrosine phosphorylation of the EGF receptor on both cell lines. Treatment of cells with a combination of IMC-C225 + gemcitabine + **radiation** produced the highest induction of apoptosis and inhibition of proliferation in vitro. Combination treatment with IMC-C225, gemcitabine, and **radiation** produced 100% complete regression of MiaPaCa-2 tumors for more than 250 days, and the greatest growth inhibition of BxPC-3 tumors compared to any single or dual treatments. Conclusions: The IMC-C225 therapy in combination with gemcitabine chemotherapy and **radiation** therapy demonstrated statistically significantly greater efficacy over the single and double combination therapies. This form of multimodality treatment shows potential clin. application in the treatment of pancreatic cancer in humans.

CC 8-9 (Radiation Biochemistry)

Section cross-reference(s): 1

ST pancreas carcinoma Erbitux EGFR antibody gemcitabine radiotherapy

IT Antibodies and Immunoglobulins

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(anti-EGFR; treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT Pancreas, neoplasm

(carcinoma; treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT Carcinoma

(pancreatic; treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT Drug interactions
(pharmacodynamic; treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT Antitumor agents
Apoptosis
Cell proliferation
Chemotherapy
Human
Phosphorylation, biological
Radiosensitizers, biological
Radiotherapy
(treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT Epidermal **growth factor** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT 62229-50-9, Epidermal **growth factor** 79079-06-4, EGFR
Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT 205923-56-4, Erbitux
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

IT 95058-81-4, Gemcitabine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and **radiation**)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:449450 HCAPLUS

DOCUMENT NUMBER: 137:706

TITLE: Combination **radiation** therapy and chemotherapy in conjunction with administration of **growth factor** receptor antibody

INVENTOR(S): Buchsbaum, Donald J.

PATENT ASSIGNEE(S): UAB Research Foundation, USA

SOURCE: PCT Int. Appl., 16 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2002045653 | A2 | 20020613 | WO 2001-US46179 | 20011207 |
| WO 2002045653 | A3 | 20030103 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
 UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002039486 A5 20020618 AU 2002-39486 20011207

US 2002076408 A1 20020620 US 2001-4833 20011207

PRIORITY APPLN. INFO.: US 2000-251787P P 20001208
 WO 2001-US46179 W 20011207

AB The invention comprises a method of inhibiting tumor growth in tumors
 having **growth factor** receptors comprising
 administering, about simultaneously, antibodies to the target
growth factor receptors, at least one chemotherapeutic
 agent, and **radiation** therapy.

IC ICM A61K

CC 1-6 (Pharmacology)
 Section cross-reference(s): 8, 15

ST chemotherapeutic radiotherapy **growth factor** receptor
 antibody combination tumor treatment

IT Antitumor agents
 Apoptosis
 Chemotherapy
 Drug interactions
 Human
 Pancreas, neoplasm
 Radiotherapy
 (chemotherapy combination with radiotherapy and **growth
 factor** receptor antibody for tumor treatment)

IT Epidermal **growth factor** receptors
Growth factor receptors
 neu (receptor)
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (chemotherapy combination with radiotherapy and **growth
 factor** receptor antibody for tumor treatment)

IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (chemotherapy combination with radiotherapy and **growth
 factor** receptor antibody for tumor treatment)

IT Intestine, neoplasm
 (colon; chemotherapy combination with radiotherapy and **growth
 factor** receptor antibody for tumor treatment)

IT Neoplasm
 (epidermoid; chemotherapy combination with radiotherapy and
growth factor receptor antibody for tumor treatment)

IT 205923-56-4, IMC-C 225
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (IMC-C 225; chemotherapy combination with radiotherapy and
growth factor receptor antibody for tumor treatment)

IT 79079-06-4, EGF receptor tyrosine kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (chemotherapy combination with radiotherapy and **growth
 factor** receptor antibody for tumor treatment)

IT 51-21-8, 5-Fluorouracil 15663-27-1, Cisplatin 23214-92-8, Doxorubicin
 33069-62-4, Paclitaxel 95058-81-4, Gemcitabine 97682-44-5, Irinotecan
 100286-90-6, CPT-11 180288-69-1, Herceptin
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(chemotherapy combination with radiotherapy and **growth factor** receptor antibody for tumor treatment)

L3 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:581735 HCAPLUS

DOCUMENT NUMBER: 135:151638

TITLE: Enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies

INVENTOR(S): **Buchsbaum, Donald J.**; Curiel, David T.; Stackhouse, Murray

PATENT ASSIGNEE(S): Uab Research Foundation, USA

SOURCE: PCT Int. Appl., 126 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--------------------------------------------------------------------------------|------|----------|-----------------|-------------|
| WO 2001056604 | A1 | 20010809 | WO 2001-US3949 | 20010207 |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |
| US 6468547 | B1 | 20021022 | US 2000-499543 | 20000207 |
| PRIORITY APPLN. INFO.: | | | US 2000-499543 | A 20000207 |
| | | | US 1996-29673P | P 19961030 |
| | | | US 1997-961327 | A2 19971030 |

AB The present invention provides a method of enhancing the chemosensitivity and radiosensitivity of a neoplastic cell expressing an oncoprotein that stimulates proliferation of the cell, comprising introducing into the cell a nucleic acid mol. encoding an antibody homolog, wherein the antibody homolog is expressed intracellularly and binds to the oncoprotein intracellularly in the endoplasmic reticulum of the cell. The present invention is also directed to a method for enhancing the inhibition of proliferation of a neoplastic cell expressing an oncoprotein that stimulates proliferation of the cell, comprising the steps of: introducing into the cell a nucleic acid mol. encoding an antibody homolog, wherein the antibody homolog is expressed intracellularly and binds to the protein intracellularly; and contacting said cell with an anti-neoplastic agent.

IC ICM A61K039-395

ICS A61K048-00; C12N015-09; C12N015-13

CC 15-3 (Immunochimistry)

Section cross-reference(s): 1, 8, 14

ST tumor chemosensitivity radiosensitivity single chain antibody

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study) (B; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)

IT Proteins, specific or class

RL: BSU (Biological study, unclassified); BIOL (Biological study) (BAG-1; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)

IT Adenoviridae

(C6.5; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)

IT Cyclins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

- (D1; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bcl-2; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Uterus, neoplasm
(cervix; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Intestine, neoplasm
(colon; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Antitumor agents
Chemotherapy
Leukemia
Lung, neoplasm
Melanoma
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Radiotherapy
Sarcoma
(enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Apoptosis
Cell cycle
Cell proliferation
DNA sequences
Plasmid vectors
Radiation
Transformation, genetic
Virus vectors
(enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT DNA
Gene, animal
Nucleoside analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Epidermal **growth factor** receptors
Growth factor receptors
Transforming proteins
neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Sarcoma
(fibrosarcoma; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments, Fab; single-chain; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)

- IT Immunoglobulins
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (fragments, Fv; single-chain; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Neuroglia
 (glioma; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Enzymes, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibitors; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)
- IT Bladder
 Digestive tract
 Mammary gland
 Prostate gland
 Salivary gland
 (neoplasm; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Bone, neoplasm
 (osteosarcoma; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Kidney, neoplasm
 (renal cell carcinoma; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Eye, neoplasm
 (retinoblastoma; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT Antibodies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
 (single chain; enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies)
- IT 51-21-8, 5-fluorouracil 127-07-1, hydroxyurea 154-93-8, bcnu 289-95-2D, pyrimidine, fluoro derivs. 289-95-2D, pyrimidine, halogenated derivs. 1404-00-8, mitomycin 11056-06-7, bleomycin 15663-27-1, cisplatin 21679-14-1, fludarabine 33069-62-4, taxol 33419-42-0, etoposide 143180-75-0
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (enhancement of tumor cell chemosensitivity and radiosensitivity using single chain secretory antibodies in relation to)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:822458 HCAPLUS

DOCUMENT NUMBER: 135:16104

TITLE: Enhanced apoptosis with combination C225/
radiation treatment serves as the impetus for
 clinical investigation in head and neck cancers

AUTHOR(S): Bonner, James A.; Raisch, Kevin P.; Trummell, Hoa Q.;

Robert, Francisco; Meredith, Ruby F.; Spencer, Sharon A.; **Buchsbaum, Donald J.**; Saleh, Mansoor N.; Stackhouse, Murray A.; LoBuglio, Albert F.; Peters, Glenn E.; Carroll, William R.; Waksal, Harlan W.

CORPORATE SOURCE: Comprehensive Cancer Center (Experimental Therapeutics Program), University of Alabama at Birmingham, Birmingham, AL, 35294-3300, USA

SOURCE: Journal of Clinical Oncology (2000), 18(21, Suppl.), 47S-53S

CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Epidermal **growth factor** receptor (EGFr) is overexpressed in a majority of head and neck squamous cell carcinomas, and this overexpression is associated with a poor prognosis. Therefore, EGFr has become the target of investigations aimed at disabling the receptor to determine whether this process leads to improved tumor kill with conventional treatment. C225 is an anti-EGFr monoclonal antibody that inhibits receptor activity by blocking the ligand binding site. A panel of human head and neck squamous cell carcinoma cell lines was used to study the combination of C225 and **radiation**. It was determined that the combination of C225 (5 µg/mL) delivered simultaneously with **radiation** (3 Gy) resulted in a greater decrement in cellular proliferation than either treatment alone. This reduction in proliferation correlated with reduced EGFr tyrosine phosphorylation and a reduction in phosphorylated signal transducer and activator of transcription-3 (STAT-3) protein (known to protect cells from apoptosis). Also, the decrement in proliferation correlated with increased apoptotic events, thereby indirectly linking C225/**radiation**-induced regulation of STAT-3 protein to apoptosis. This preclin. work serves as important support for the ongoing clin. investigation of C225 and radiotherapy for patients with head and neck carcinomas. The initial results of these clin. studies have been promising.

CC 8-9 (Radiation Biochemistry)

ST head neck squamous carcinoma radiotherapy antiEGFr antibody; epidermal **growth factor** receptor squamous carcinoma radiotherapy

IT Transcription factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(STAT3; effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Apoptosis

Radiotherapy

(effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Epidermal **growth factor** receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Antitumor agents

(head and neck squamous cell carcinoma; effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Antibodies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(monoclonal, C225; effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Head
Neck, anatomical
(squamous cell carcinoma, inhibitors; effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

IT Head
Neck, anatomical
(squamous cell carcinoma; effect of combined radiotherapy and anti-EGFr monoclonal antibody on head and neck cancers)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:29947 HCAPLUS

DOCUMENT NUMBER: 132:290547

TITLE: Combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and radiation

AUTHOR(S): Saleh, Mansoor N.; Raisch, Kevin P.; Stackhouse, Murray A.; Grizzle, William E.; Bonner, James A.; Mayo, Matthew S.; Kim, Hyung-Gyoon; Meredith, Ruby F.; Wheeler, Richard H.; **Buchsbaum, Donald J.**

CORPORATE SOURCE: Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, 35294, USA

SOURCE: Cancer Biotherapy & Radiopharmaceuticals (1999), 14(6), 451-463

CODEN: CBRAFJ; ISSN: 1084-9785

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background. Monoclonal antibodies (mAb) to epidermal **growth factor** receptor (EGFr) inhibit tumor cell proliferation and enhance cytotoxicity of chemotherapeutic agents. The purpose of this study was to investigate the interaction of the anti-EGFr antibody C225 combined with radiotherapy (RT) on EGFr expressing A431 human epidermoid cancer cells. Methods. Cell proliferation, apoptosis, EGFr expression and phosphorylation, and clonogenic survival were assayed in vitro. A431 tumor growth inhibition and immunohistochem. anal. of EGFr expression and apoptosis were assessed in vivo. Results. C225 plus RT produced greater inhibition of A431 cell proliferation than C225 or RT alone which was corroborated by enhanced apoptosis. Similar clonogenic survival occurred following the addition of C225 to RT, although colonies were smaller in the presence of C225. C225 produced inhibition of EGF-induced phosphorylation of EGFr without concurrent down-regulation of surface receptor, which was not altered by RT. Combined treatment of mice bearing tumors demonstrated enhancement of complete regressions, reduction in time to tumor size doubling, and prolongation of survival. Significant apoptosis occurred in xenograft tumors treated with C225 with or without RT. Conclusions. These data demonstrate an interaction between C225 and RT. C225-mediated apoptosis and inhibition of EGFr phosphorylation may be critical in the interaction. Studies to define the precise influence of combined modality treatment on the EGFr signal transduction cascade need to be pursued. The combination of **growth factor** receptor antibodies and RT has potential application in clin. oncol.

CC 8-9 (Radiation Biochemistry)

ST epidermoid cancer radiotherapy antiEGFr antibody

IT Antibodies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(chimeric; combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and **radiation**)

IT Radiotherapy

(combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and **radiation**)

IT Epidermal **growth factor** receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and **radiation**)

IT Antitumor agents

(squamous cell carcinoma; combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and **radiation**)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:753259 HCAPLUS

DOCUMENT NUMBER: 132:2792

TITLE: Treatment of human tumors with **radiation** and antibodies to **growth factor** receptor kinases

INVENTOR(S): Waksal, Harlan W.; Saleh, Mansoor N.; Robert, Francisco; **Buchsbaum, Donald Jay**

PATENT ASSIGNEE(S): Imclone Systems Incorporated, USA; UAB Research Foundation

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|-------------|
| WO 9960023 | A1 | 19991125 | WO 1999-US10741 | 19990514 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2332331 | AA | 19991125 | CA 1999-2332331 | 19990514 |
| AU 9940799 | A1 | 19991206 | AU 1999-40799 | 19990514 |
| EP 1080113 | A1 | 20010307 | EP 1999-924253 | 19990514 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| BR 9910511 | A | 20011120 | BR 1999-10511 | 19990514 |
| JP 2002515511 | T2 | 20020528 | JP 2000-549641 | 19990514 |
| ZA 2000007412 | A | 20020312 | ZA 2000-7412 | 20001212 |
| US 2004057950 | A1 | 20040325 | US 2003-661881 | 20030911 |
| PRIORITY APPLN. INFO.: | | | US 1998-79612 | A 19980515 |
| | | | US 1998-85613P | P 19980515 |
| | | | US 1998-206138 | A 19981207 |
| | | | US 1999-312286 | B3 19990514 |
| | | | WO 1999-US10741 | W 19990514 |

AB The authors disclose a treatment regimen to inhibit the growth of tumors in human patients. The regimen comprises the co-administration of **radiation** and a non-radiolabeled protein receptor tyrosine kinase inhibitor (e.g., monoclonal antibodies). In one example, human patients were treated with anti-EGF receptor chimeric antibody c225 along with external beam **radiation**.

IC ICM C07K016-00
ICS A61K039-395

CC 15-3 (Immunochemistry)
Section cross-reference(s): 2, 8, 14

ST antitumor **radiation** receptor tyrosine kinase inhibitor

IT Antitumor agents
(bladder; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)

IT Antitumor agents
Antitumor agents
(brain; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chimeric; to **growth factor** receptor tyrosine kinases for combination therapy of human tumors)

IT Intestine, neoplasm
Intestine, neoplasm
(colon, inhibitors; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)

IT Antitumor agents
(colon; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)

IT Antitumor agents
(combination therapy of **radiation** and inhibitors of **growth factor** receptor tyrosine kinases as)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments, hypervariable region; to **growth factor** receptor tyrosine kinases for combination therapy of human tumors)

IT Antitumor agents
(head; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)

IT **Growth factor** receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(heregulin, ErbB-3; tumor therapy with **radiation** and antibodies to)

IT **Growth factor** receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(heregulin, ErbB-4; tumor therapy with **radiation** and antibodies to)

IT **Growth factor** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heregulin, ErbB-4; tumor therapy with **radiation** and antibodies to)

IT **Growth factor** receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(heregulin, erbB-3; tumor therapy with **radiation** and antibodies to)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; to **growth factor** receptor tyrosine

- kinases for combination therapy of human tumors)
- IT Radiotherapy
 - (in combination with inhibitors of **growth factor** receptor tyrosine kinases for tumor therapy)
- IT Brain, neoplasm
 - Brain, neoplasm
 - Kidney, neoplasm
 - Kidney, neoplasm
 - Lung, neoplasm
 - Lung, neoplasm
 - Ovary, neoplasm
 - Ovary, neoplasm
 - (inhibitors; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antitumor agents
 - Antitumor agents
 - (kidney; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antitumor agents
 - Antitumor agents
 - (lung; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antitumor agents
 - (mammary gland; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antibodies
 - RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (monoclonal; to **growth factor** receptor tyrosine kinases for combination therapy of human tumors)
- IT Antitumor agents
 - (neck; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Bladder
 - Bladder
 - Head
 - Head
 - Mammary gland
 - Mammary gland
 - Neck, anatomical
 - Neck, anatomical
 - Prostate gland
 - Prostate gland
 - (neoplasm, inhibitors; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antitumor agents
 - Antitumor agents
 - (ovary; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Antitumor agents
 - (prostate gland; combination therapy with **radiation** and antibodies to **growth factor** receptor tyrosine kinases as)
- IT Phosphorylation, biological
 - (protein; of EGF receptor is inhibited by monoclonal antibodies in relation to combination therapy of human tumors)
- IT Epidermal **growth factor** receptors

Insulin-like **growth factor** I receptors
 Nerve **growth factor** receptors
 Transforming **growth factor** receptors
 neu (receptor)
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (tumor therapy with **radiation** and antibodies to)

IT **Growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (tumor therapy with **radiation** and inhibitors of)

IT Fibroblast **growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (type 1; tumor therapy with **radiation** and antibodies to)

IT Fibroblast **growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (type 2; tumor therapy with **radiation** and antibodies to)

IT Fibroblast **growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (type 3; tumor therapy with **radiation** and antibodies to)

IT Fibroblast **growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (type 4; tumor therapy with **radiation** and antibodies to)

IT Platelet-derived **growth factor** receptors
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (α ; tumor therapy with **radiation** and antibodies to)

IT 250741-11-8, PN: WO9960023 SEQID: 5 unclaimed DNA
 RL: PRP (Properties)
 (Unclaimed; treatment of human tumors with **radiation** and
 antibodies to **growth factor** receptor kinases)

IT 79079-06-4, EGF receptor tyrosine kinase 136396-12-8, Platelet-derived
growth factor receptor β tyrosine kinase
 137010-36-7, NGF receptor tyrosine kinase 137632-09-8 147014-95-7,
 C-ErbB-3 protein kinase 150027-15-9, Fibroblast **growth**
factor receptor 1 tyrosine kinase 150027-21-7, Platelet-derived
growth factor receptor α tyrosine kinase
 150316-06-6, FGF receptor kinase type 2
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (tumor therapy with **radiation** and antibodies to)

IT 127407-08-3, Receptor tyrosine kinase
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (tumor therapy with **radiation** and inhibitors of)

IT 250741-00-5, 1: PN: WO9960023 SEQID: 1 unclaimed DNA 250741-10-7, 2: PN:
 WO9960023 SEQID: 3 unclaimed DNA 250741-12-9, 3: PN: WO9960023 SEQID: 7
 unclaimed DNA 250741-14-1, 4: PN: WO9960023 SEQID: 9 unclaimed DNA
 250741-17-4, 5: PN: WO9960023 SEQID: 11 unclaimed DNA
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; treatment of human tumors with
radiation and antibodies to **growth factor**
 receptor kinases)

IT 155661-31-7 186759-74-0
 RL: PRP (Properties)
 (unclaimed protein sequence; treatment of human tumors with
radiation and antibodies to **growth factor**
 receptor kinases)

IT 250718-27-5 250718-28-6 250718-29-7 250718-31-1
 RL: PRP (Properties)
 (unclaimed sequence; treatment of human tumors with **radiation**
 and antibodies to **growth factor** receptor kinases)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT